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Patent- og Varemærkestyrelsen
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Pia Høybye-Olsen

PATENT- OG VAREMÆRKESTYRELSEN

COMPOUNDS FOR USE IN TREATING OBESITY

FIELD OF INVENTION

The present invention relates to novel compounds, pharmaceutical compositions containing them, use of the compounds for preparing medicaments for appetite regulation or for treating obesity and obesity related diseases as well as to a method for treatment of obesity and, consequently, for the treatment of obesity related diseases and conditions such as atherosclerosis, hypertension, diabetes, especially type 2 diabetes (NIDDM (non-insulin dependent diabetes mellitus)), impaired glucose tolerance (IGT), dyslipidaemia, coronary heart disease, gallbladder disease, osteoarthritis and various types of cancer such as endometrial, breast, prostate and colon cancers and the risk for premature death as well as other conditions, such as diseases and disorders, which conditions are improved by activation of the melanocortin receptors.

BACKGROUND OF THE INVENTION

Obesity is a well known risk factor for the development of many very common diseases such as atherosclerosis, hypertension, type 2 diabetes (non-insulin dependent diabetes mellitus (NIDDM)), dyslipidaemia, coronary heart disease, and osteoarthritis and various malignancies. It also causes considerable problems through reduced motility and decreased quality of life. The incidence of obesity and thereby also these diseases is increasing throughout the entire industrialised world. Only a few pharmacological treatments are available to date, namely Sibutramine (acting via serotonergic and noradrenaline mechanisms, Abbott) and Orlistat (reducing fat uptake from the gut, Roche Pharm). However, due to the important effect of obesity as a risk factor in serious and even mortal and common diseases there is still a need for pharmaceutical compounds useful in the treatment of obesity.

The term obesity implies an excess of adipose tissue. In this context obesity is best viewed as any degree of excess adiposity that imparts a health risk. The distinction between normal and obese individuals can only be approximated, but the health risk imparted by obesity is probably a continuum with increasing adiposity. However, in the context of the present invention, individuals with a body mass index (BMI = body weight in kilograms divided by the square of the height in meters) above 25 are to be regarded as obese.

Even mild obesity increases the risk for premature death, diabetes, hypertension, atherosclerosis, gallbladder disease and certain types of cancer. In the industrialised western world the prevalence of obesity has increased significantly in the past few decades. Because

of the high prevalence of obesity and its health consequences, its treatment should be a high public health priority.

When energy intake exceeds energy expenditure, the excess calories are stored in adipose tissue, and if this net positive balance is prolonged, obesity results, i.e. there are two components to weight balance, and an abnormality on either side (intake or expenditure) can lead to obesity.

Pro-opiomelanocortin (POMC) is the precursor for β-endorphin and melanocortin peptides, including melanocyte stimulating hormone (α-MSH) and adrenocorticotropin (ACTH). POMC is expressed in several peripheral and central tissues including melanocytes, pituitary and neurones of the hypothalamus. The POMC precursor is processed differently in different tissues resulting in the expression of different melanocortin peptides depending on the site of expression. In the anterior lobe of the pituitary, mainly ACTH is produced whereas in the intermediate lobe and the hypothalamic neurones the major peptides are α-MSH, β-MSH, desacetyl-α-MSH and β-endorphin. Several of the melanocortin peptides, including ACTH and α-MSH, have been demonstrated to have appetite suppressing activity when injected intracerebroventricular in rats (Vergoni et al, European Journal of Pharmacology 179, 347-355 (1990)).

A family of five melanocortin receptor subtypes has been identified (melanocortin receptor 1-5, also called MC1, MC2, MC3, MC4 and MC5). The MC1, MC2 and MC5 are mainly expressed in peripheral tissues whereas MC3 and MC4 are mainly centrally expressed. The MC4 receptor is shown to be involved in the regulation of body weight and feeding behaviour as MC4 knock out mice develop obesity (Huzar et al, Cell 88, 131-141 (1997)). Furthermore studies of either ectopic centrally expression of agouti (MC1, MC3 and MC4 antagonist) or over-expression of an endogenously occurring MC3 and MC4 antagonist (agouti gene related peptide, AGRP) in the brain demonstrated that the over-expression of these two antagonists lead to the development of obesity (Kleibig et al, PNAS 92, 4728-4732 (1995)). Furthermore icv injection of a C-terminal fragment of AGRP increases feeding and antagonises the inhibitory effect of α-MSH on food intake.

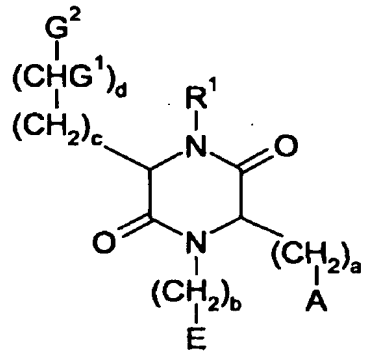
In humans several case of families with obesity presumably due to frame shift mutations in the MC4 receptor have been described (e.g. Yeo et al, Nature Genetics 20, 111-112 (1998), Vaisse et al, Nature Genetics 20, 113-114).

In conclusion a MC4 agonist could serve as an anorectic drug, and be useful in the treatment of obesity or obesity related diseases as well as in the treatment of other diseases, disorders or conditions, which are improved by activation of the MC4 receptor.

MC4 antagonists may be useful for treatment of cachaxia, anorexia, and for treatment of waisting in frail elderly patients. Furthermore MC4 antagonists may be used for treatment of chronic pain, neuropathy and neurogenic inflammation.

SUMMARY OF THE INVENTION

The present invention relates to novel compounds of the general formula (I),



Formula (I)

wherein

A is $-NR^2R^3$ or guanidinyl, the last optionally substituted with C_{1-6}-alkyl, wherein

R^2 and R^3 independently of each other are hydrogen, C_{1-6}-alkyl, C_{1-6}-alkylene-$N(R^{11})(R^{12})$, C_{1-6}-alkylene-CN, C_{1-6}-alkylene-OH, C_{1-6}-alkylene-$C(O)$-$N(R^{11})(R^{12})$, $(Z^1)_e$-R^{13}, or $-CO$-R^{14}, wherein

R^{11} and R^{12} independently of each other are hydrogen or C_{1-6}-alkyl;

Z^1 is C_{1-6}-alkylene;

e is an integer selected from 0 or 1;

R^{13} is cycloalkyl, heterocyclyl, aryl, or heteroaryl; each of which may be optionally substituted with a substitutent selected from the group consisting of C_{1-6}-alkyl, amino, and $-CO-O-Z^4-R^{23}$, wherein

Z^4 is C_{1-6}-alkylene; and

R^{23} is aryl; and

R^{14} is hydrogen, C_{1-6}-alkyl, $-N(R^{15})(R^{16})$, C_{1-6}-alkylene-$N(R^{15})(R^{16})$, $C(R^{17})(R^{18})$-$N(R^{19})(R^{20})$, heterocyclyl, $(Z^2)_f$-R^{21}, heteroaryl, or C_{1-6}-alkoxy, wherein

R^{15} and R^{16} independently of each other are hydrogen, or C_{1-6}-alkyl;

R^{17} and R^{18} independently of each other are hydrogen, C_{1-6}-alkylene-NH_2 or $(Z^3)_g$-R^{22}), wherein

Z^3 is C_{1-6}-alkylene;

g is an integer selected from 0 or 1; and

R^{22} is cycloalkyl, heterocyclyl, aryl or heteroaryl;

R^{19} and R^{20} independently of each other are hydrogen, C_{2-6}-alkylene-NH_2, C_{1-6}-alkylene-CF_3 or cycloalkyl; and

Z^2 is C_{1-6}-alkylene;

f is an integer selected from 0 or 1; and

R^{21} is cycloalkyl, heterocyclyl, aryl or heteroaryl;

a is an integer selected from 1, 2, 3, 4, or 5;

E is cycloalkyl, heterocyclyl, aryl or heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, -NR^4R^5, -CO-R^6, C_{1-6}-alkyl, C_{1-6}-alkoxy, trifluoromethyl, trifluoromethoxy, and –L^1-Q^1, wherein

R^4 and R^5 independently of each other are hydrogen, C_{1-6}-alkyl, -CO-R^{24}, or aryl, wherein

R^{24} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy;

R^6 is C_{1-6}-alkyl or C_{1-6}-alkoxy;

L^1 is a direct bond, -CH_2-, -O-, -CO-, -CH_2-O-, -O-CH_2- or –NR^{25}-, wherein

R^{25} is hydrogen or C_{1-6}-alkyl; and

Q^1 is cycloalkyl, heterocyclyl, aryl or heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, -$NR^{26}R^{27}$, -CO-R^{28}, -$S(O)_2$-R^{29}, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl and C_{3-7}-cycloalkoxy, wherein

R^{26} and R^{27} independently of each other are hydrogen, C_{1-6}-alkyl, or -CO-R^{30}, wherein

R^{30} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy;

R^{28} is C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{29} is C_{1-6}-alkyl, -NH-C_{1-6}-alkyl, or -N(C_{1-6}-alkyl)$_2$;

or

Q^1 is L^3-R^{31}, wherein

L^3 is -CH_2-, -O-, -CO-, -CH_2-O-, -O-CH_2-, -CH_2-O-C(O)-, or -C(O)-O-CH_2-; and

R^{31} is aryl or heteroaryl;

b is an integer selected from 0, 1, or 2;

G^1 is C_{1-6}-alkyl, C_{1-6}-alkoxy, cycloalkyl, C_{3-7}-cycloalkoxy, aryl or heteroaryl; each of which may be optionally substituted with halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, -NR^7R^8, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkoxy, wherein

R^7 and R^8 independently of each other are hydrogen, C_{1-6}-alkyl, aryl, heteroaryl, -CO-R^{32} or -SO_2-R^{33}, wherein

R^{32} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{33} is C_{1-6}-alkyl, -NH-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)$_2$;

G^2 is cycloalkyl, heterocyclyl, aryl, or heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -NR^9R^{10}, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkoxy or –L^2-Q^2, wherein

R^9 and R^{10} are independently hydrogen, C_{1-6}-alkyl, aryl, heteroaryl, -CO-R^{34} or -SO_2-R^{35}, wherein

R^{34} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{35} is C_{1-6}-alkyl, -NH-C_{1-6}-alkyl, or -N(C_{1-6}-alkyl)$_2$;

L^2 is a direct bond, -CH_2-, -O-, -CO-, -CH_2-O-, -O-CH_2- or –NR^{36}-, wherein

R^{36} is hydrogen or C_{1-6}-alkyl; and

Q^2 is cycloalkyl, heterocyclyl, aryl or heteroaryl; each of which may be optionally substituted with halogen, hydroxy, cyano, nitro, trifluoromethyl, -$NR^{37}R^{38}$, -CO-R^{39}, -O-R^{40}, C_{1-6}-alkyl, C_{1-6}-hydroxyalkyl, C_{3-7}-cycloalkyl or C_{3-7}-cycloalkoxy, wherein

R^{37} and R^{38} independently of each other are hydrogen, C_{1-6}-alkyl or -CO-R^{41}, wherein

R^{41} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy;

R^{39} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{40} is C_{1-6}-alkyl or trifluoromethyl;

c is an integer selected from 0, 1, or 2;

d is an integer selected from 0, or 1;and

R^1 is hydrogen, alkyl, alkenyl, or alkynyl;

well as any optical or geometric isomer or tautomer form thereof,

or a pharmaeutically acceptable salt thereof.

The present invention also relates to pharmaceutical compositions containing compounds according to the present invention, use of compounds according to the present invention for preparing medicaments for appetite regulation or for treating obesity and obesity related diseases and to a method for treatment of obesity and, consequently, for the treatment of obesity related diseases and conditions such as atherosclerosis, hypertension, diabetes, especially type 2 diabetes (NIDDM (non-insulin dependent diabetes mellitus)), impaired glucose tolerance, dyslipidaemia, coronary heart disease, gallbladder disease, osteoarthritis and various types of cancer such as endometrial, breast, prostate and colon

cancers and the risk for premature death as well as other conditions, such as diseases and disorders, which conditions are improved by activation of the MC4 receptor.

The present invention also relates to use of compounds according to the present invention for preparing medicaments for increasing skin pigmentation, for protecting the skin against ultraviolet radiation (UVR) and for inhibiting the effects of UVR, for protecting the skin against local skin irritants (e.g. bacterial lipopolysaccharide), for modulating the inflammatory responses in the skin, for functionally antagonising the actions of proinflammatory cytokines produced in the skin after a local irritation, for regulating the immune response, for preventing contact dermatitis, and for inhibiting chronic inflammatory responses.

The present invention also relates to use of compounds according to the present invention for regulating glucocorticoid production.

The present invention also relates to use of compounds according to the present invention for reducing blood pressure and heart rate and for inducing natriuresis.

The present invention also relates to use of compounds according to the present invention for regulating exocrine gland secretion, for regulating aldosterone secretion and thereby regulating blood pressure and natriuresis, for suppressing stress-induced alarm substances, and for stimulating exocrine glands, cardiac and testicular functions.

The present invention also relates to use of compounds according to the present invention for treating sexual dysfunction.

The present invention also relates to use of compounds according to the present invention for increasing antipyretic activity.

The present invention also relates to use of compounds according to the present invention for inducing lipolysis.

The present invention also relates to use of compounds according to the present invention for treating chronic pain.

ABBREVIATIONS

aq.	aqueous
Boc	*tert*-butyloxycarbonyl
Cbz	benzyloxycarbonyl
CDI	N,N'-carbonyldiimidazole
conc.	concentrated
DCM	dichloromethane
DIC	N,N'-diisopropylcarbodiimide
DIPEA	N,N-diisopropyl-ethyl-amine
DMF	N,N-Dimethylformamide

equi	equivalent
FMOC/fmoc	9-fluorenylmethyloxycarbonyl
h	hour/hours
HOBt	1-hydroxybenzotriazole monohydrate
i No.	intermediate number
LCMS	liquid chromatography coupled with mass spectrometry
min.	minutes
NMP	N-methyl pyrrolidone
TBDPS	*tert*-butyl diphenylsilyl
TBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TFA	trifluoroacetic acid
TBDPS	*tert*-butyl diphenylsilyl
THF	tetrahydrofurane
org.	organic
Rt or R_t	retention time
RT	room temperature
sat.	saturated

DEFINITIONS

In the above structural formulas and throughout the present specification, the following terms have the indicated meaning:

"Halogen" designates an atom selected from the group consisting of F, Cl, Br or I.

The use of prefixes of this structure: C_{x-y}-alkyl, C_{x-y}-alkenyl, C_{x-y}-alkynyl, C_{x-y}-cycloalyl or C_{x-y}-cycloalkyl-C_{x-y}-alkenyl- designates radical of the designated type having from x to y carbon atoms.

The term "alkyl" as used herein, alone or in combination, refers to a straight or branched chain saturated monovalent hydrocarbon radical having from one to ten carbon atoms, for example C_{1-8}-alkyl. Typical C_{1-8}-alkyl groups include, but are not limited to e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, 2-methylbutyl, 3-methylbutyl, 4-methylpentyl, neopentyl, n-pentyl, n-hexyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1,2,2-trimethylpropyl and the like. The term "C_{1-8}-alkyl" as used herein also includes secondary C_{3-8}-alkyl and tertiary C_{4-8}-alkyl.

The term "C_{1-6}-alkyl" as used herein, alone or in combination, represents a straight or branched chain saturated monovalent hydrocarbon radical containing from 1 to 6 carbons atoms. Representative examples for "C_{1-6}-alkyl" include, but are not limited to, methyl, ethyl,

n-propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, n-pentyl, isopentyl, neopentyl, *tert*-pentyl, n-hexyl, isohexyl and the like. Similarly the term "C_{1-18}-alkyl" represent a straight or branched carbon chain containing from 1 to 18 carbons atoms.

The term "alkylene" as used herein, alone or in combination, refers to a straight or branched chain saturated divalent hydrocarbon radical having from one to ten carbon atoms, for example C_{1-8}-alkylene. Examples of "alkylene" as used herein include, but are not limited to, methylene, ethylene, and the like.

The term "alkoxy" as used herein, alone or in combination, refers to the monovalent radical R^aO-, where R^a is alkyl as defined above, for example C_{1-8}-alkyl giving C_{1-8}-alkoxy. Typical C_{1-8}-alkoxy groups include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, *sec*-butoxy, *tert*-butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

The term "C_{1-6}-alkoxy" as used herein, alone or in combination, refers to the monovalent radical C_{1-6}-alkyl-O-, where C_{1-6}-alkyl is as defined above. Representative examples are methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, *sec*-butoxy, *tert*-butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy and the like.

The term "cycloalkyl" as used herein, alone or in combination, refers to a non-aromatic monovalent hydrocarbon radical having from three to twelve carbon atoms, and optionally with one or more degrees of unsaturation, for example C_{3-8}-cycloalkyl. Such a ring may be optionally fused to one or more benzene rings or to one or more of other cycloalkyl ring(s). Typical C_{3-8}-cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl and the like.

The term "C_{3-6}-cycloalkyl" as used herein, alone or in combination, refers to a non-aromatic monovalent hydrocarbon radical having from 3 to 6 carbon atoms. Representative examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "heterocyclic" or the term "heterocyclyl" as used herein, alone or in combination, refers to a heterocyclic ring with for instance three to thirteen member atoms, for example C_{3-10}-heterocyclyl, such as C_{3-8}-heterocyclyl, having one or more degrees of unsaturation containing one or more heteroatomic substitutions selected from S, SO, SO_2, O, or N, for example selected from N, O, or S. Such a ring may be optionally fused to one or more of another "heterocyclic" ring(s) or cycloalkyl ring(s). Representative examples of C_{3-10}-heterocyclyl or C_{3-8}-heterocyclyl groups include, but are not limited to, pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, aziridinyl, tetrahydrofuranyl and the like.

The term "aryl" as used herein, alone or in combination, refers to a carbocyclic aromatic ring radical or to a aromatic ring system radical with for instance six to thirteen member atoms, such as phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl,

indenyl, pentalenyl, azulenyl, biphenylenyl, 5H-dibenzo[a,d]cyclohepten-5-yl, 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl and the like. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl and the like.

The term "aryloxy" as used herein denotes a group aryl-O-, wherein aryl is as defined above.

The term "heteroaryl", as used herein, alone or in combination, refers to an aromatic ring radical with for instance 5 to 7 member atoms, or to an aromatic ring system radical with for instance from 7 to 18 member atoms, containing one or more heteroatoms selected from nitrogen, oxygen, or sulfur heteroatoms, wherein N-oxides and sulfur monoxides and sulfur dioxides are permissible heteroaromatic substitutions; such as e.g. furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5- triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuryl, benzothienyl, naphtothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl, dibenzo[b,f]azepin-5-yl, 10,11-dihydro-dibenzo[b,f]azepin-5-yl and the like. Heteroaryl is also intended to include the partially hydrogenated derivatives of the heterocyclic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 2,3-dihydrobenzofuranyl, pyrrolinyl, pyrazolinyl, indolinyl, oxazolidinyl, oxazolinyl, oxazepinyl and the like.

The term "hydroxyalkyl" as used herein, alone or in combination, represents an alkyl radical as described above, such as a C_{1-6}-alkyl, substituted with one or more hydroxy radicals. Examples of C_{1-6}-hydroxyalkyl radicals are 2-hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, 3-hydroxypropyl, 2,3-dihydroxypropyl and the like.

The term "optionally substituted" as used herein means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified. When the groups in question are substituted with more than one substituent the substituents may be the same or different.

Certain of the above defined terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the other.

"Selective" or "selectivity" towards the MC1 receptor, when used herein with regard to a compound of the present invention being an agonist of said receptor, means that the

compound does not bind or activate the other MC receptors, that is MC2, MC3, MC4 and MC5. Likewise, a compound being a selective agonist of the MC2 receptor means that the compound does not bind or activate the other MC receptors, that is MC1, MC3, MC4 and MC5. Likewise, a compound being a selective agonist of the MC3 receptor means that the compound does not bind or activate the other MC receptors, that is MC1, MC2, MC4 and MC5. Likewise, a compound being a selective agonist of the MC4 receptor means that the compound does not bind or activate the other MC receptors, that is MC1, MC2, MC3 and MC5. Likewise, a compound being a selective agonist of the MC5 receptor means that the compound does not bind or activate the other MC receptors, that is MC1, MC2, MC3 and MC4. A compound according to the present invention may also be said to be selective for two receptors, such as for instance the MC3 and MC4 receptor, meaning that the compound does not bind or activate the other MC receptors, in this case MC1, MC2, and MC5.

A "therapeutically effective amount" of a compound according to the present invention as used herein means an amount sufficient to cure, alleviate or partially arrest the clinical manifestations of a given disease and its complications. An amount adequate to accomplish this is defined as "therapeutically effective amount". Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix.

The term "treatment" and "treating" as used herein means the management and care of a patient for the purpose of combating a condition, such as a disease or a disorder. The term is intended to include the full spectrum of treatments for a given condition from which the patient is suffering, such as administration of the active compound to alleviate the symptoms or complications, to delay the progression of the disease, disorder or condition, to alleviate or relief the symptoms and complications, and/or to cure or eliminate the disease, disorder or condition as well as to prevent the condition, wherein prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of the active compounds to prevent the onset of the symptoms or complications. The patient to be treated is preferably a mammal, in particular a human being.

DESCRIPTION OF THE FIGURE

Figur 1: Effect on food intake in schedule fed (8h-13h) male SPRD rat model as described in assay 1 . The rats are dosed ip at 08.00 h with vehicle, sibutramine (3 mg/kg) and (S,S)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-piperazine-2,5-

dione (example 11) (1, 3 or 10 mg/kg). Rat chow and water is available from just post dosing, and food intake is measured every hour from dosing to 3 hours post dosing.

The bars indicate the cumulated food intake over time.

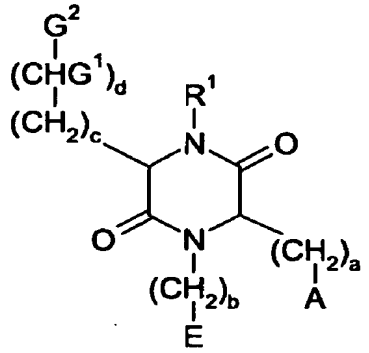
DESCRIPTION OF THE INVENTION

It is an object of the present invention to provide novel compounds being effective in appetite regulation and/or in the treatment of obesity or obesity related diseases such as atherosclerosis, hypertension, diabetes, especially type 2 diabetes (NIDDM (non-insulin dependent diabetes mellitus)), dyslipidaemia, coronary heart disease, gallbladder disease, osteoarthritis and various types of cancer such as endometrial, breast, prostate and colon cancers and the risk for premature death as well as other other conditions, such as diseases and disorders, which conditions are improved by activation of the MC4 receptor.

It is a further object of the present invention to provide pharmaceutical compositions comprising the novel compounds of the invention being effective against obesity or obesity related diseases as described above as well as other conditions, such as diseases and disorders, which conditions are improved by activation of the MC4 receptor.

Further objects will become apparent from the following description.

In one aspect, the invention relates to compounds according to formula (I)



Formula (I)

wherein

A is $-NR^2R^3$ or guanidinyl, the last optionally substituted with C_{1-6}-alkyl, wherein

R^2 and R^3 independently of each other are hydrogen, C_{1-6}-alkyl, C_{1-6}-alkylene-$N(R^{11})(R^{12})$, C_{1-6}-alkylene-CN, C_{1-6}-alkylene-OH, C_{1-6}-alkylene-$C(O)$-$N(R^{11})(R^{12})$, $(Z^1)_e$-R^{13}, or -CO-R^{14}, wherein

R^{11} and R^{12} independently of each other are hydrogen or C_{1-6}-alkyl;

Z^1 is C_{1-6}-alkylene;

e is an integer selected from 0 or 1;

R^{13} is cycloalkyl, heterocyclyl, aryl, or heteroaryl; each of which may be optionally substituted with a substitutent selected from the group consisting of C_{1-6}-alkyl, amino, and -CO-O-Z^4-R^{23}, wherein

Z^4 is C_{1-6}-alkylene; and

R^{23} is aryl; and

R^{14} is hydrogen, C_{1-6}-alkyl, -N(R^{15})(R^{16}), C_{1-6}-alkylene-N(R^{15})(R^{16}), C(R^{17})(R^{18})-N(R^{19})(R^{20}), heterocyclyl, (Z^2)$_f$-R^{21}, heteroaryl, or C_{1-6}-alkoxy, wherein

R^{15} and R^{16} independently of each other are hydrogen, or C_{1-6}-alkyl;

R^{17} and R^{18} independently of each other are hydrogen, C_{1-6}-alkylene-NH_2 or (Z^3)$_g$-R^{22}), wherein

Z^3 is C_{1-6}-alkylene;

g is an integer selected from 0 or 1; and

R^{22} is cycloalkyl, heterocyclyl, aryl or heteroaryl;

R^{19} and R^{20} independently of each other are hydrogen, C_{2-6}-alkylene-NH_2, C_{1-6}-alkylene-CF_3 or cycloalkyl; and

Z^2 is C_{1-6}-alkylene;

f is an integer selected from 0 or 1; and

R^{21} is cycloalkyl, heterocyclyl, aryl or heteroaryl;

a is an integer selected from 1, 2, 3, 4, or 5;

E is cycloalkyl, heterocyclyl, aryl or heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, -NR^4R^5, -CO-R^6, C_{1-6}-alkyl, C_{1-6}-alkoxy, trifluoromethyl, trifluoromethoxy, and –L^1-Q^1, wherein

R^4 and R^5 independently of each other are hydrogen, C_{1-6}-alkyl, -CO-R^{24}, or aryl, wherein

R^{24} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy;

R^6 is C_{1-6}-alkyl or C_{1-6}-alkoxy;

L^1 is a direct bond, -CH_2-, -O-, -CO-, -CH_2-O-, -O-CH_2- or –NR^{25}-, wherein

R^{25} is hydrogen or C_{1-6}-alkyl; and

Q^1 is cycloalkyl, heterocyclyl, aryl or heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, -$NR^{26}R^{27}$, -CO-R^{28}, -S(O)$_2$-R^{29}, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl and C_{3-7}-cycloalkoxy, wherein

R^{26} and R^{27} independently of each other are hydrogen, C_{1-6}-alkyl, or -CO-R^{30}, wherein

R^{30} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy;

R^{28} is C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{29} is C_{1-6}-alkyl, -NH-C_{1-6}-alkyl, or -N(C_{1-6}-alkyl)$_2$;

or

Q^1 is L^3-R^{31}, wherein

L^3 is -CH_2-, -O-, -CO-, -CH_2-O-, -O-CH_2-, -CH_2-O-C(O)-, or -C(O)-O-CH_2-; and

R^{31} is aryl or heteroaryl;

b is an integer selected from 0, 1, or 2;

G^1 is C_{1-6}-alkyl, C_{1-6}-alkoxy, cycloalkyl, C_{3-7}-cycloalkoxy, aryl or heteroaryl; each of which may be optionally substituted with halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, -NR^7R^8, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkoxy, wherein

R^7 and R^8 independently of each other are hydrogen, C_{1-6}-alkyl, aryl, heteroaryl, -CO-R^{32} or -SO_2-R^{33}, wherein

R^{32} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{33} is C_{1-6}-alkyl, -NH-C_{1-6}-alkyl, -N(C_{1-6}-alkyl)$_2$;

G^2 is cycloalkyl, heterocyclyl, aryl, or heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, -NR^9R^{10}, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkoxy or –L^2-Q^2, wherein

R^9 and R^{10} are independently hydrogen, C_{1-6}-alkyl, aryl, heteroaryl, -CO-R^{34} or -SO_2-R^{35}, wherein

R^{34} is hydrogen; C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{35} is C_{1-6}-alkyl, -NH-C_{1-6}-alkyl, or -N(C_{1-6}-alkyl)$_2$;

L^2 is a direct bond, -CH_2-, -O-, -CO-, -CH_2-O-, -O-CH_2- or –NR^{36}-, wherein

R^{36} is hydrogen or C_{1-6}-alkyl; and

Q^2 is cycloalkyl, heterocyclyl, aryl or heteroaryl; each of which may be optionally substituted with halogen, hydroxy, cyano, nitro, trifluoromethyl, -$NR^{37}R^{38}$, -CO-R^{39}, -O-R^{40}, C_{1-6}-alkyl, C_{1-6}-hydroxyalkyl, C_{3-7}-cycloalkyl or C_{3-7}-cycloalkoxy, wherein

R^{37} and R^{38} independently of each other are hydrogen, C_{1-6}-alkyl or -CO-R^{41}, wherein

R^{41} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy;

R^{39} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{40} is C_{1-6}-alkyl or trifluoromethyl;

c is an integer selected from 0, 1, or 2;

d is an integer selected from 0, or 1;and

R^1 is hydrogen, alkyl, alkenyl, or alkynyl;

as well as any optical or geometric isomer or tautomer form thereof,

or a pharmaeutically acceptable salt thereof.

Further embodiments of the compounds of the present invention are clear from the appended claims.

The compounds of the present invention may have one or more asymmetric centres and it is intended that stereoisomers (optical isomers), as separated, pure or partially purified stereoisomers or racemic mixtures thereof are included in the scope of the invention.

Diastereomers, enantiomers and tautomeric forms of compounds of general formula (I) including mixtures of these or pharmaceutically acceptable salts thereof are also within the scope of the present invention

In one embodiment of the present invention, the compound is an agonist of a melanocortin receptor, such as the MC4 receptor.

In one embodiment of the present invention, the compound is an intermediate in the synthesis of a agonist of a melanocortin receptor, such as the MC4 receptor.

In a further embodiment, the compound is selective for the MC4 receptor.

In one embodiment, the present invention relates to a pharmaceutical composition comprising, as an active ingredient, at least one compound according to the present invention together with one or more pharmaceutically acceptable carriers or excipients.

In one embodiment, the present invention relates to a pharmaceutical composition comprising, as an active ingredient, at least one compound according to the present invention together with one or more pharmaceutically acceptable carriers or excipients in unit dosage form, comprising from about 0.05 mg to about 1000 mg, such as about 0.1 mg to about 500 mg, for example from about 0.5 mg to about 200 mg of a compound according to the present invention.

In one embodiment, the present invention relates to the use of a compound according to the present invention for increasing the activity of the MC4 receptor.

In one embodiment, the present invention relates to the use of a compound according to the present invention for the delaying or prevention of the progression from IGT to type 2 diabetes.

In one embodiment, the present invention relates to the use of a compound according to the present invention for the preparation of a medicament for the delaying or prevention of the progression from IGT to type 2 diabetes.

In one embodiment, the present invention relates to the use of a compound according to the present invention for the delaying or prevention of the progression from non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes.

In one embodiment, the present invention relates to the use of a compound according to the present invention for the preparation of a medicament for the delaying or prevention of the progression from non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes.

In one embodiment, the present invention relates to the use of a compound according to the present invention for treating a condition which is improved by the activation of the MC4 receptor.

In one embodiment, the present invention relates to the use of a compound according to the present invention for the preparation of a medicament for treating a condition which is improved by the activation of the MC4 receptor.

In one embodiment, the present invention relates to the use of a compound according to the present invention for appetite regulation.

In one embodiment, the present invention relates to the use of a compound according to the present invention for treating a condition related to overweight or obesity.

In one embodiment, the present invention relates to the use of a compound according to the present invention for the preparation of a medicament for appetite regulation.

In one embodiment, the present invention relates to the use of a compound according to the present invention for the preparation of a medicament for treating a condition related to overweight or obesity.

In one embodiment, the present invention relates to the use of a compound according to the present invention for treating a disease or condition selected from overweight or obesity, atherosclerosis, hypertension, diabetes, type 2 diabetes, impaired glucose tolerance, dyslipidaemia, coronary heart disease, gallbladder disease, osteoarthritis, cancer, sexual dysfunction and the risk for premature death in a patient in need thereof.

In one embodiment, the present invention relates to the use of a compound according to the present invention for the preparation of a medicament for treating a disease or condition selected from overweight or obesity, atherosclerosis, hypertension, diabetes, type 2 diabetes, impaired glucose tolerance, dyslipidaemia, coronary heart disease, gallbladder disease, osteoarthritis, cancer, sexual dysfunction and the risk for premature death in a patient in need thereof.

In one embodiment, the present invention relates to the use of a compound according to the present invention for treating overweight or obesity.

In one embodiment, the present invention relates to the use of a compound according to the present invention for the preparation of a medicament for treating overweight or obesity.

In one embodiment, the present invention relates to the use of a compound according to the present invention for treating type 2 diabetes, for instance in obese patients.

In one embodiment, the present invention relates to the use of a compound according to the present invention for the preparation of a medicament for treating type 2 diabetes, for instance in obese patients.

In one embodiment, the present invention relates to the use of a compound according to the present invention for treating dyslipidemia, for instance in obese patients.

In one embodiment, the present invention relates to the use of a compound according to the present invention for the preparation of a medicament for treating dyslipidemia, for instance in obese patients.

In one embodiment, the present invention relates to the use of a compound according to the present invention for treating sexual dysfunction.

In one embodiment, the present invention relates to the use of a compound according to the present invention for the preparation of a medicament for treating sexual dysfunction.

In one embodiment, the present invention relates to the use of a compound according to the present invention for reducing the weight of a subject.

In one embodiment, the present invention relates to the use of a compound according to the present invention for the preparation of a medicament for reducing the weight of a subject.

In one embodiment, the present invention relates to the use of a compound according to the present invention for the suppression of appetite or for satiety induction.

In one embodiment, the present invention relates to the use of a compound according to the present invention for the preparation of a medicament for the suppression of appetite or for satiety induction.

In one embodiment, the present invention relates to the use of a compound according to the present invention for treatment of eating disorders such as bulimia and binge eating.

In one embodiment, the present invention relates to the use of a compound according to the present invention for the preparation of a medicament for treatment of eating disorders such as bulimia and binge eating.

In one aspect, the invention relates to a method for the treatment of disorders related to melanocortin MC4 receptor, the method comprising administering to a subject in need thereof an effective amount of a compound according to formula (I)

In a still further aspect, the invention relates to a method for the treatment of obesity, the method comprising administering to a subject in need thereof an effective amount of a compound according to formula (I) or a pharmaceutically acceptable salt thereof, or of a composition according to any one of the preceding composition claims.

In still another aspect, the invention relates to a method for the treatment of diabetes, preferably type 2 diabetes, the method comprising administering to a subject in need thereof an effective amount of a compound according to formula (I) or a pharmaceutically acceptable salt thereof, or of a composition according to any one of the preceding composition claims.

In still another aspect, the invention relates to the use of a compound according to formula (I) or a pharmaceutically acceptable salt thereof for the preparation of a medicament.

Furthermore the invention relates to the use of a compound according to formula (I) or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of disorders related to melanocortin MC4 receptor.

More particular the invention relates to the use of a compound according formula (I) or a pharmaceutically acceptable salt thereof for the preparation of a medicament having melanocortin MC4 agonist activity.

The invention relates furthermore to the use of a compound according to formula (I) or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of obesity.

The invention relates furthermore to the use of a compound according to formula (I) or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of diabetes preferably type 2 diabetes. Such treatment includes inter alia treatment for the purpose of delaying or prevention of the progression from IGT to type 2 diabetes as well as delaying or prevention of the progression from non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes.

The invention relates furthermore to the use of a compound according to formula (I) or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of obesity and complications related to obesity and excessive food consumption and other eating disorders and specific complications related to obesity, such as hypertension, dyslipidemia, diabetes mellitus, coronary heart disease, congestive heart failure, stroke, gallstones, osteoarthritis, sleep apnea, cancer, women's health/reproduction (within this area is noted psychopathology of obesity, such as body image and binge eating).

Further more the compounds according to formula (I) may be useful for stimulation of melanin-production, skin darkening, inflammation, body temperature, pain perception, neuropathy, blood pressure, heart rate, vascular tone, natruresis, brain blood flow, nerve growth, placental development, aldosteron synthesis and release, thyroxin release, spermatogenesis, ovarian weight, prolactin, growth hormone and FSH secretion, uterine bleeding in women, sebum and pheromone secretion, blood glucose levels, intrauterine foetal growth, as well as other related to parturition, and to afford neuroprotective effects and for the treatment of eating disorders, improvement of libido activity in male and female and for stimulation of penile erection as well as psychiatric disorders, (such as depression, anxiety, motivational defects, cognitive disorders, memory loss and other psychiatric disorders as known by those skilled in the art), as well as addiction.

The present invention also provides pharmaceutical compositions comprising as an active ingredient, at least one compound, preferably in a pharmacologically effective amount, more preferably in a therapeutically effective amount, suitable for any of the uses according to the present invention together with one or more pharmaceutically acceptable carriers or excipients.

In a use or a method according to the present invention, a compound according to the present invention may also be administered in combination with one or more further active substances in any suitable ratios. Such further active agents may be selected from antidiabetic agents, antihyperlipidemic agents, antiobesity agents, antihypertensive agents and agents for the treatment of complications resulting from or associated with diabetes.

Suitable antidiabetic agents include insulin, GLP-1 (glucagon like peptide-1) derivatives such as those disclosed in WO 98/08871 (Novo Nordisk A/S), which is incorporated herein by reference, as well as orally active hypoglycemic agents.

Suitable orally active hypoglycemic agents include imidazolines, sulfonylureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, insulin sensitizers, α-glucosidase inhibitors, agents acting on the ATP-dependent potassium channel of the pancreatic β-cells eg potassium channel openers such as those disclosed in WO 97/26265, WO 99/03861 and WO 00/37474 (Novo Nordisk A/S) which are incorporated herein by reference, potassium channel openers, such as ormitiglinide, potassium channel blockers such as nateglinide or BTS-67582, glucagon antagonists such as those disclosed in WO 99/01423 and WO 00/39088 (Novo Nordisk A/S and Agouron Pharmaceuticals, Inc.), all of which are incorporated herein by reference, GLP-1 agonists such as those disclosed in WO 00/42026 (Novo Nordisk A/S and Agouron Pharmaceuticals, Inc.), which are incorporated herein by reference, DPP-IV (dipeptidyl peptidase-IV) inhibitors, PTPase (protein tyrosine phosphatase) inhibitors, glucokinase activators, such as those described in WO 02/08209 to

Hoffmann La Roche, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, GSK-3 (glycogen synthase kinase-3) inhibitors, compounds modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents, compounds lowering food intake, and PPAR (peroxisome proliferator-activated receptor) and RXR (retinoid X receptor) agonists such as ALRT-268, LG-1268 or LG-1069.

In one embodiment of the uses and methods of the present invention, the compound involved may be administered in combination with insulin or insulin analogues.

In one embodiment of the uses and methods of the present invention, the compound involved may be administered in combination with a sulphonylurea eg tolbutamide, chlorpropamide, tolazamide, glibenclamide, glipizide, glimepiride, glicazide or glyburide.

In one embodiment of the uses and methods of the present invention, the compound involved may be administered in combination with a biguanide eg metformin.

In one embodiment of the uses and methods of the present invention, the compound involved may be administered in combination with a meglitinide eg repaglinide or senaglinide/nateglinide.

In one embodiment of the uses and methods of the present invention, the compound involved may be administered in combination with a thiazolidinedione insulin sensitizer eg troglitazone, ciglitazone, pioglitazone, rosiglitazone, isaglitazone, darglitazone, englitazone, CS-011/CI-1037 or T 174 or the compounds disclosed in WO 97/41097 (DRF-2344), WO 97/41119, WO 97/41120, WO 00/41121 and WO 98/45292 (Dr. Reddy's Research Foundation), which are incorporated herein by reference.

In one embodiment of the uses and methods of the present invention, the compound involved may be administered in combination with an insulin sensitizer eg such as GI 262570, YM-440, MCC-555, JTT-501, AR-H039242, KRP-297, GW-409544, CRE-16336, AR-H049020, LY510929, MBX-102, CLX-0940, GW-501516 or the compounds disclosed in WO 99/19313 (NN622/DRF-2725), WO 00/50414, WO 00/63191, WO 00/63192, WO 00/63193 (Dr. Reddy's Research Foundation) and WO 00/23425, WO 00/23415, WO 00/23451, WO 00/23445, WO 00/23417, WO 00/23416, WO 00/63153, WO 00/63196, WO 00/63209, WO 00/63190 and WO 00/63189 (Novo Nordisk A/S), which are incorporated herein by reference.

In one embodiment of the uses and methods of the present invention, the compound involved may be administered in combination with an α-glucosidase inhibitor eg voglibose, emiglitate, miglitol or acarbose.

In one embodiment of the uses and methods of the present invention, the compound involved may be administered in combination with a glycogen phosphorylase inhibitor eg the compounds described in WO 97/09040 (Novo Nordisk A/S).

In one embodiment of the uses and methods of the present invention, the compound involved may be administered in combination with a glucokinase activator.

In one embodiment of the uses and methods of the present invention, the compound involved may be administered in combination with an agent acting on the ATP-dependent potassium channel of the pancreatic β-cells eg tolbutamide, glibenclamide, glipizide, glicazide, BTS-67582 or repaglinide.

In one embodiment of the uses and methods of the present invention, the compound involved may be administered in combination with nateglinide.

In one embodiment of the uses and methods of the present invention, the compound involved may be administered in combination with an antihyperlipidemic agent or a antilipidemic agent eg cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

In one embodiment of the uses and methods of the present invention, the compound involved may be administered in combination with more than one of the above-mentioned compounds eg in combination with metformin and a sulphonylurea such as glyburide; a sulphonylurea and acarbose; nateglinide and metformin; acarbose and metformin; a sulfonylurea, metformin and troglitazone; insulin and a sulfonylurea; insulin and metformin; insulin, metformin and a sulfonylurea; insulin and troglitazone; insulin and lovastatin; etc.

In one embodiment of the uses and methods of the present invention, the compound involved may be administered in combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, β3 adrenergic agonists such as CL-316243, AJ-9677, GW-0604, LY362884, LY377267 or AZ-40140, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin reuptake inhibitors (fluoxetine, seroxat or citalopram), serotonin and norepinephrine reuptake inhibitors, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth factors such as prolactin or placental lactogen, growth hormone releasing compounds, TRH (thyreotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA (dopamine) agonists (bromocriptin, doprexin),

lipase/amylase inhibitors, PPAR modulators, RXR modulators, TR β agonists, adrenergic CNS stimulating agents, AGRP (agouti related protein) inhibitors, H3 histamine antagonists such as those disclosed in WO 00/42023, WO 00/63208 and WO 00/64884, which are incorporated herein by reference, exendin-4, GLP-1 agonists and ciliary neurotrophic factor. Further antiobesity agents are bupropion (antidepressant), topiramate (anticonvulsant), ecopipam (dopamine D1/D5 antagonist), naltrexone (opioid antagonist), and peptide YY_{3-36} (Batterham et al, Nature 418, 650-654 (2002)).

In one embodiment, the antiobesity agent is leptin.

In one embodiment, the antiobesity agent is peptide YY_{3-36}.

In one embodiment, the antiobesity agent is a serotonin and norepinephrine reuptake inhibitor eg sibutramine.

In one embodiment, the antiobesity agent is a lipase inhibitor eg orlistat.

In one embodiment, the antiobesity agent is an adrenergic CNS stimulating agent eg dexamphetamine, amphetamine, phentermine, mazindol phendimetrazine, diethylpropion, fenfluramine or dexfenfluramine.

Furthermore, in the uses and methods of the present invention, the compound involved may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are β-blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and α-blockers such as doxazosin, urapidil, prazosin and terazosin. Further reference can be made to Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

It should be understood that any suitable combination of the compounds according to the invention with diet and/or exercise, one or more of the above-mentioned compounds and optionally one or more other active substances are considered to be within the scope of the present invention.

Other embodiments of the present invention are clear from the appended claims.

PHARMACEUTICAL COMPOSITIONS

In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of the general formula (I) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

Optionally, the pharmaceutical composition of the invention may comprise a compound of formula (I) combined with one or more compounds.

Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, buccal, subdermal, intradermal, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain a compound of formula (I) dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tabletting techniques may contain:

Core:	
Active compound (as free compound or salt thereof)	250 mg
Colloidal silicon dioxide (Aerosil)®	1.5 mg
Cellulose, microcryst. (Avicel)®	70 mg
Modified cellulose gum (Ac-Di-Sol)®	7.5 mg
Magnesium stearate	**Ad.**
Coating:	
HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, such as prevention, elimination, alleviation or amelioration of obesity. Such mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

The compounds of the invention may be effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 1000 mg, for example from about 0.1 to about 500 mg, such as from about 0.5 mg to about 250 mg per day may be used. In choosing a regimen for patients it may frequently be necessary to begin with a higher dosage and when the condition is under control to reduce the dosage. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge. A dosage of for instance from 1 to 100 mg/kg body weight, for example 10 mg/kg body weight pr day may be used.

Generally, the compounds of the present invention are dispensed in unit dosage form comprising from about 0.05 to about 1000 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration comprise from about 0.05 mg to about 1000 mg, such as from about 0.5 mg to about 250 mg of the compounds of formula (I) admixed with a pharmaceutically acceptable carrier or diluent.

Any novel feature or combination of features described herein is contemplated within the scope of this invention.

EXAMPLES

HPLC-MS (Method A)

The following instrumentation is used:

- SciexAPI 100 Single quadropole mass spectrometer
- Perkin Elmer Series 200 Quard pump
- Perkin Elmer Series 200 autosampler
- Applied Biosystems 785A UV detector
- Sedex55 evaporative light scattering detector

A Valco column switch with a Valco actuator controlled by timed events from the pump.

The instrument control and data acquisition are done by the SciexSample control software running on a Macintosh PowerPC 7200 computer.

The HPLC pump is connected to four eluent reservoirs containing:

A: acetonitrile

B: water

C: 0.5% TFA in water

D: 0.02 M ammonium acetate

The requirements for samples are that they contain approximately 500 µg/ml of the compound to be analysed in an acceptable solvent such as methanol, ethanol, acetonitrile, THF, water and mixtures thereof. (High concentrations of strongly eluting solvents will interfere with the chromatography at low acetonitrile concentration.)

The analysis is performed at room temperature by injecting 20 µl of the sample solution on the column which is eluted with a gradient of acetonitrile in either 0.05% TFA or 0.002 M ammonium acetate. Depending on the analysis method varying elution conditions are used.

The eluate from the column is passed through a flow splitting T-connector which passed approximately 20 µl/min (1/50) through approx. 1 m. 75 µm fused silica capillary to the API interface of API 100 spectrometer.

The remaining 1.48 ml/min (49/50) is passed through the UV detector and to the ELS detector.

During the LC-analysis the detection data are acquired concurrently from mass spectrometer, UV detector and ELS detector.

The LC conditions, detector settings and mass spectrometer settings used for the different methods are given in the following tables.

Column	Waters Symmetry C_{18} 3 mmx150 mm			
Gradient	5% - 90% acetonitrile in 0.05% TFA linearly during 15 min at 1 ml/min			
Detection	UV: 214 nm		ELS: 40°C	
MS	Experiment:	Start: 100 amu	Stop: 800 amu	Step: 0.2 amu
	Dwell:	0.571 msec		
	Method:	Scan 284 times = 9.5 min		

HPLC-MS (Method B)

This method is identical to HPLC-MS (Method A) but using the following conditions and settings:

Column	YMC ODS-A 120Å s - 5µ 50 mmx3 mm id			
Gradient	5% - 90% acetonitrile in 0.05% TFA linearly during 7.5 min at 1.5 ml/min			
Detection	UV: 214 nm		ELS: 40°C	
MS	Experiment:	Start: 100 amu	Stop: 800 amu	Step: 0.2 amu
	Dwell:	0.571 msec		
	Method:	Scan 284 times = 9.5 min		

HPLC-MS (Method C)

The following instrumentation is used:

- Hewlett Packard series 1100 G1312A Bin Pump
- Hewlett Packard series 1100 Column compartment
- Hewlett Packard series 1100 G13 15A DAD diode array detector
- Hewlett Packard series 1100 MSD

The instrument is controlled by HP Chemstation software.

The HPLC pump is connected to two eluent reservoirs containing:

A: 0.01% TFA in water

B: 0.01% TFA in acetonitrile

The analysis is performed at 40°C by injecting an appropriate volume af the sample (preferably 1 µl) onto the column which is eluted with a gradient of acetonitrile.

The HPLC conditions, detector settings and mass spectrometer settings usded are giving in the following table.

Column	Waters Xterra MS C-18x3 mm id
Gradient	10% - 100% acetonitrile lineary during 7.5 min at 1.0 ml/min
Detection	210 nm (analog output from DAD)
MS	ionisation mode API-ES Scan 100-1000 amu step 0.1 amu

HPLC-MS (Method D)

The following instrumentation is used:

- Hewlett Packard series 1100 G1312A Bin Pump
- Hewlett Packard series 1100 G13 15A DAD diode array detector
- Sciex3000 triplequadropole mass spectrometer
- Gilson 215 micro injector
- Sedex55 evaporative light scattering detector

Pumps and detectors are controlled by MassChrom 1.1.1 software running on a MacIntosh G3 computer. Gilson Unipoint Version 1.90 controls the auto-injector.

The HPLC pump is connected to two eluent reservoirs containing:

A: 0.01% TFA in water

B: 0.01% TFA in acetonitrile

The analysis is performed at room temperature by injecting an appropriate volume of the sample (preferably 10 µl) onto the column, which is eluted, with a gradient of acetonitrile. The eluate from the column passed through the UV detector to meet a flow splitter, which passed approximately 30 µl/min (1/50) through to the API Turbo ion-spray

interface of API 3000 spectrometer. The remaining 1.48 ml/min (49/50) is passed through to the ELS detector.

The HPLC conditions, detector settings and mass spectrometer settings used are giving in the following table.

Column	Waters X-Terra C18, 5µ, 50 mmx3 mm id
Gradient	5% - 90% acetonitrile linearly during 7.5 min at 1.5 ml/min
Detection	210 nm (analogue output from DAD)
MS	ionisation mode API Turbo ion-spray Scan 100-1000 amu step 0.1 amu
ELS	Gain 8 and 40°C

GENERAL PROCEDURES

General procedure (A) - Synthesis on solid phase, suitable for the synthesis of multiple examples in parallel

Step A:

Add 9 equi. of Fmoc protected amino acid, 1 equi. of DMAP and 4 equi. of DIPEA dissolved in 1000 µl DCM to 50 mg polystyrene resin loaded with the Wang-linker (1 mmol/g) in a suitable reaction vessel.

Add 4 equi. of DIC in 500 µl DCM, shake the vessel for 12 h and then wash the resin 6 times with 1800 µl DCM.

Step B:

Add 1500 µl of a 1:1 mixture of DMF and piperidine to the resin, shake for 30 min and wash 6 times with 1800 µl DMF.

Step C:

Add 5 equi. of aldehyde in 1000 µl NMP and 100 µl HOAc to the resin and shake the vessel for 12 h. Remove the liquid phase and add 1500 µl 0.5 M $NaCNBH_3$ in MeOH/DCM 1:1. Shake the vessel for another 12 h. Wash the resin twice with 1800 µl MeOH, twice with 1700 µl DCM, 100 µl DIPEA and twice with 1800 µl DCM.

Step D:

Add 8 equi. of Boc-protected amino acid in 1000 µl THF and 4 equi. DIC in 500 µl to the resin and shake for 30 min. Add 50 µl DIPEA and shake for another 12 h. Remove the liquid phase by suction and repeat the procedure. Afterwards the resin is washed once with 1800 µl DMF and 10 times with 1800 µl DCM. The product is cleaved from the resin with 1500 µl TFA/DCM 1:1. After evaporation *in vacuo* of the solvent, the residual oil is taken up

in 1 ml toluene and heated for 1 h to 60°C. The solvent is again removed *in vacuo* and the sample analysed by HPLC.

General procedure (B) Solution phase synthesis

Step A:

10 mmol amino acid methyl ester hydrochloride, 1 equi. aldehyde and 1 equi. DIPEA are suspended in 100 ml THF and the resulting mixture is stirred overnight. Then 2.9 equi. $NaCNBH_3$, 10 ml MeOH and 5 ml HOAc are added and stirred for 3 h. The solvent is removed *in vacuo* and the residual oil is taken up in 100 ml ethyl acetate. The org. phase is washed once with 100 ml 1M NaOH. The aq. phase is extracted once with 100 ml ethyl acetate and the combined org. phases are dried over sodium sulfate. The solvent is removed *in vacuo* and the crude product is used for the next step.

Step B:

18.4 mmol Boc-protected amino acid is dissolved in 50 ml THF, 0.5 equi. DIC is added and the resulting mixture is stirred for 20 min. Then the crude product of step A is added in 50 ml THF and stirred for 2 h. Another 0.25 equi. DIC is added and after 20 min 2 ml of DIPEA. The solvent is removed after 3 h of stirring and the residue is taken up in 100 ml ethyl acetate. The org. phase is washed with 100 ml 1 M HCl and 100 ml sat. $NaHCO_3$ and dried over sodium sulfate. The solvent is removed *in vacuo* and the residual oil is purified on silica with ethyl acetate/heptane.

Step C:

The purified product from step B is dissolved in 100 ml DCM and 100 ml TFA is added. The solvents are removed after 2 h. The residual oil is taken up in 100 ml toluene and the solvent is again removed *in vacuo*. The oil is taken up in 100 ml DCM and 1 ml DIPEA is added. The solvent is removed *in vacuo* and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

General procedure (C) - Synthesis on solid phase, suitable for the synthesis of multiple examples in parallel

Step A:

A linker on polystyrene is prepared by stirring 20 g hydroxymethyl polystyrene (loading 0.87 mmol/g) with 11.3 g (4 equi.) carbonyldiimidazol (CDI) in 500 ml tetrahydrofuran (THF) for 17 h. Wash the resin then with dichloromethane and take it up in 500 ml N-methyl pyrrolidone (NMP). Add 5.3 ml (4 equi) amino propanol and stirr the mixture over night. Wash the resin once with methanol and once with dichloromethane. Repeat the

two washing steps twice (3x(1xMeOH,1xCH_2Cl_2)). Wash the resin once with diethylether and dry it *in vacuo*.

Step B:

Add 9 equi. of fmoc protected amino acid and 1 equi. of DMAP dissolved in 2000 µl THF to 50 mg polystyrene resin from step A in a suitable reaction vessel. Add 4 equi. of DIC, shake the vessel for 17 h and then wash the resin 2 times with 3000 µl NMP.

Step C:

Add 1000 µl NMP and 1000 µl piperidine and shake the mixture for 30 min. Wash the resin 5 times with 3000 µl NMP.

Step D:

Add 5 equi. aldehyde in 1500 µl NMP and 100 µl HOAc and shake the mixture for 6 h. Remove the liquid phase by suction and add 2000 µl of 0.5 M $NaCNBH_3$ in MeOH/DCM 1:1. Shake over night and wash the resin twice with 3000 µl MeOH, twice with 3000 µl DCM+100 µl DIPEA and twice with 3000 µl DCM.

Step E:

Add 8 equi. Boc-protected amino acid in 1500 µl THF and 4 equi. DIC. Shake the resin for 30 min and add 50 µl DIPEA. Shake for another 4 h and remove the liquid phase by suction. Add again 8 equi. Boc-protected amino acid in 1500 µl THF and 4 equi. DIC. Shake the resin for 30 min and add 50 µl DIPEA. Shake overnight and wash twice with 3000 µl NMP and 5 times with 3000 µl DCM. Add 1000 µl DCM and 1000µl TFA and shake for 30 min. Wash the resin 5 times with 3000 µl DCM and twice with 3000 µl MeOH. Cleave the product from the resin with 1000 µl DCM and 1000 µl 33% $MeNH_2$ in ethanol for 1 h. The solvent is removed in a nitrogen stream and the samples are taken up in MeOH and analysed by HPLC-MS.

General Procedure (D) Mitsunobu reaction on a diketopiperazine

Step A:

A intermediate product is synthesised according to general procedure B using Boc-Tyr(*t*-bu)-OH for the acylation in step C.

Step B:

The product of step A (14 mmol) is dissolved in 100 ml DCM and 2 equi., 6.1 ml Boc-anhydrid and 1 equi., 2.4 ml DIPEA are added. The solvent is removed *in vacuo* and the product is purified and silica.

Step C:

The product of step B (1 mmol) is dissolved in 10 ml THF and 1 equi., 0.3 g triphenylphosphine and 1 equi. alcohol are added. Then 1 equi., 160 µl diethyl azadicarboxylate are added and the mixture is stirred over night. The solvent is removed *in vacuo* and the product is purified either on reverse phase or silica.

Step D:

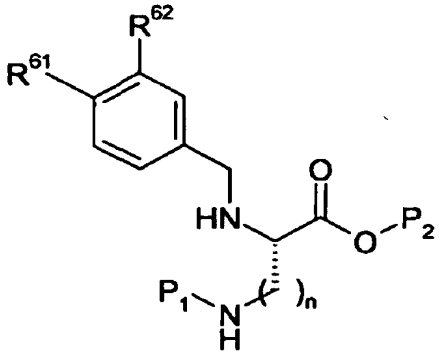
The product of step C (0.5 mmol) is dissolved in 25 ml DCM and 25 ml TFA. The solvent is removed after 30 min and the solvents are removed *in vacuo*. The product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

General Procedure (E): Ester method

Step A:

To *ω-N*-protected amino acid methyl ester hydrochloride (10 mmol) and aldehyde (10.3 mmol) in THF (80 ml) is added at room temperature sodium triacetoxyborohydride (11 mmol) and the mixture is stirred overnight. Sat. aq. potassium carbonate (100 ml) is added and the mixture is stirred for 1 h. The layers are separated and the aq. layer is extracted with ethyl acetate (3x100 ml). The combined org. layers are dried over sodium sulfate and evaporated *in vacuo*. Flash chromatography (silica, dichloromethane) afforded the product.

Examples of intermediate compounds of the formula below prepared according to the general procedure E, step A, are shown below.



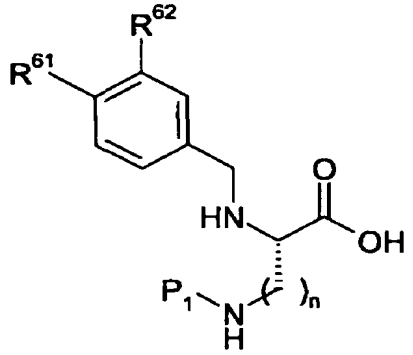
i No.	R^{61}	R^{62}	P_1	P_2	n	Yield	ESI-MS $(M+H)^+$
i1	Ph	H	Boc	Me	1	80%	385
i2	OPh	H	Boc	Me	1	98%	401
i3	H	OPh	Boc	Me	1	59%	401
i4	Ph	H	Cbz	Me	1	77%	419
i5	OPh	H	Cbz	Me	1	70%	435
i6	Ph	H	Boc	Me	2	62%	399
i7	OPh	H	Boc	Me	2	63%	415

i No.	R^{61}	R^{62}	P_1	P_2	n	Yield	ESI-MS $(M+H)^+$
i8	Ph	H	Cbz	Me	3	48%	447
i9	Br	H	Boc	Me	4	quant.	430
i10	Ph	H	Boc	Me	4	68%	427
i11	OPh	H	Boc	Me	4	37%	443
i12	Bn	H	Boc	Me	4	42%	441
i13	OBn	H	Boc	Me	4	38%	457
i14	OBn	H	Boc	t-Bu	4	85%	499
i15	N(Me)Ph	H	Boc	Me	4	61%	456
i16	OCbz	H	Boc	Me	4	56%	501
i17	OTBDPS	H	Boc	Me	4	45%	605
i18	OPh	Me	Boc	Me	4	43%	457
i19	OPh	OMe	Boc	Me	4	56%	473
i20	O-4-pyridyl	H	Boc	Me	4	31%	444
i21	Ph	H	Cbz	Me	4	65%	461
i22	OPh	H	Cbz	Me	4	19%	477
i23	Ph	H	Cbz	Me	5	45%	475

Step B:

To *ω-N*-protected amino acid methyl ester hydrochloride (10 mmol) in MeOH / THF 1:1 (60 ml) is added at room temperature lithium hydroxide hydrate (40 mmol) in water (30 ml) and the mixture is stirred overnight. The mixture is diluted with water (100 ml) and acidified with sat. aq. potassium bisulfate (200 ml). The precipitate is collected by filtration, washed with water (3x50 ml), and dried at 60°C to give the free acid product.

Examples of intermediate compounds of the formula below prepared according to the general procedure E, step B, are shown below:



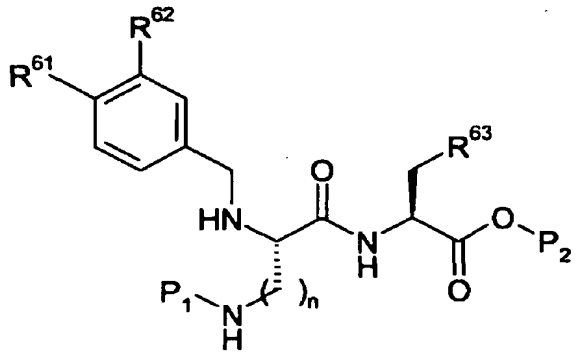
i No.	R^{61}	R^{62}	P_1	n	Yield	ESI-MS $(M+H)^+$
i24	Ph	H	Boc	1	86%	371
i25	OPh	H	Boc	1	90%	387
i26	H	OPh	Boc	1	83%	387
i27	Ph	H	Cbz	1	91%	405
i28	OPh	H	Cbz	1	89%	421
i29	Ph	H	Boc	2	77%	385
i30	OPh	H	Boc	2	94%	401
i31	Ph	H	Cbz	3	70%	433

i No.	R^{61}	R^{62}	P_1	n	Yield	ESI-MS $(M+H)^+$
i32	Ph	H	Boc	4	94%	413
i33	OPh	H	Boc	4	96%	429
i34	O-4-pyridyl	H	Boc	4	60%	430
i35	OPh	H	Cbz	4	92%	463

Step C:

To the product of general procedure E, step B (10 mmol), amino acid methyl ester (10 mmol), TBTU (10.4 mmol), and HOBt (10.2 mmol) in THF (150 ml) is added N-ethyldiisopropylamine (35 mmol) and the mixture is stirred at room temperature overnight. The mixture is concentrated *in vacuo* and diluted with ethyl acetate (150 ml). The org. layer is washed with sat. aq. sodium carbonate (3x) and water (2x), dried over sodium sulfate, and evaporated *in vacuo*. Flash chromatography (silica, petroleum ether / ethyl acetate 1:1 → ethyl acetate / MeOH 49:1) afforded the product.

Examples of intermediate compounds of the formula below prepared according to the general procedure E, step C, are shown below:



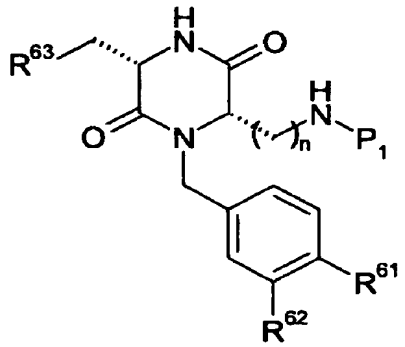
i No.	R^{61}	R^{62}	R^{63}	P_1	P_2	n	Yield	ESI-MS $(M+H)^+$
i36	Ph	H	2-naphthyl	Boc	Me	1	89%	582
i37	OPh	H	2-naphthyl	Boc	Me	1	quant	598
i38	H	OPh	2-naphthyl	Boc	Me	1	86%	598
i39	OPh	H	3,4-Cl_2-C_6H_3	Boc	Me	1	91%	617
i40	OPh	H	4-CF_3-C_6H_4	Boc	Me	1	quant	616
i41	OPh	H	4-OCF_3-3-Cl-C_6H_3	Boc	Et	1	78%	681
i42	OPh	H	4-OCF_3-C_6H_4	Boc	Et	1	74%	646
i43	OPh	H	4-OCF_2H-C_6H_4	Boc	Et	1	80%	628
i44	Ph	H	2-naphthyl	Cbz	Me	1	92%	616
i45	OPh	H	2-naphthyl	Cbz	Me	1	95%	632
i46	Ph	H	2-naphthyl	Boc	Me	2	81%	596
i47	OPh	H	2-naphthyl	Boc	Me	2	87%	612
i48	Ph	H	2-naphthyl	Cbz	Me	3	87%	644
i49	Ph	H	2-naphthyl	Boc	Me	4	86%	624
i50	OPh	H	5,6,7,8-tetrahydro-naphthalen-2-yl	Boc	Me	4	70%	644
i51	OPh	H	4-NH_2-3,5-Br_2-C_6H_2	Boc	Me	4	96%	763

i No.	R^{61}	R^{62}	R^{63}	P_1	P_2	n	Yield	ESI-MS $(M+H)^+$
i52	OPh	H	4-OH-3,5-Br_2-C_6H_2	Boc	Me	4	96%	764
i53	OPh	H	4-MeO-3-Cl-C_6H_3	Boc	Me	4	99%	655
i54	O-4-pyridyl	H	2-naphthyl	Boc	Me	4	83%	641
i55	Ph	H	1-MeO-naphthalen-2-yl	Boc	Et	4	45%	668
i56	Ph	H	6-Cl-naphthalen-2-yl	Boc	Et	4	94%	673
i57	OPh	H	3,4-Et_2-C_6H_3	Boc	Me	4	99%	646

Step D:

The product of general procedure E, step C (5 mmol) in toluene/n-butanol/glacial acetic acid 5:5:1 (200 ml) is heated to reflux for 24 h, concentrated *in vacuo*, and diluted with ethyl acetate (200 ml). The org. layer is washed with sat. aq. sodium carbonate (2x) and water (1x), dried over sodium sulfate, and evaporated *in vacuo*. Flash chromatography (silica, petroleum ether/ethyl acetate 3:1 → 1:3) afforded the product.

Examples of intermediate compounds of the formula below prepared according to the general procedure E, step D, are shown below:



i No.	R^{61}	R^{62}	R^{63}	P_1	n	Yield	ESI-MS
i58	Ph	H	2-naphthyl	Boc	1	98%	$(M-H)^-$ = 548
i59	Ph	H	2-naphthyl	Cbz	1	quant	$(M+H)^+$ = 584
i60	OPh	H	2-naphthyl	Boc	1	crude	$(M-H)^-$ = 564
i61	H	OPh	2-naphthyl	Boc	1	quant	$(M-H)^-$ = 564
i62	OPh	H	4-OCF_3-C_6H_4	Boc	1	78%	$(M-H)^-$ = 598
i63	OPh	H	4-OCF_2H-C_6H_4	Boc	1	92%	$(M-H)^-$ = 580
i64	OPh	H	4-OCF_3-3-Cl-C_6H_3	Boc	1	40%	$(M-H)^-$ = 632
i65	OPh	H	3,4-Cl_2-C_6H_3	Boc	1	92%	$(M+Na)^+$= 606
i66	OPh	H	4-CF_3-C_6H_4	Boc	1	quant	$(M+H)^+$ = 584
i67	Ph	H	2-naphtyl	Boc	2	83%	$(M-H)^-$ = 562
i68	OPh	H	2-naphthyl	Boc	2	90%	$(M+H)^+$ = 580
i69	Ph	H	2-naphthyl	Cbz	3	97%	$(M-H)^-$ = 610
i70	Ph	H	2-naphthyl	Boc	4	50%	$(M-H)^-$ = 646
i71	Ph	H	1-MeO-naphthalen-2-yl	Boc	4	69%	$(M+H)^+$ = 622
i72	Ph	H	6-Cl-naphthalen-2-yl	Boc	4	quant	$(M+H)^+$ = 626
i73	OPh	H	3,4-Et_2-C_6H_3	Boc	4	quant	$(M+H)^+$ = 614
i74	OPh	H	4-MeO-3-Cl-C_6H_3	Boc	4	99%	$(M+H)^+$ = 623
i75	OPh	H	4-NH_2-3,5-Br_2-C_6H_2	Boc	4	64%	$(M-H)^-$ = 727
i76	OPh	H	4-OH-3,5-Br_2-C_6H_2	Boc	4	76%	$(M+H)^+$ = 730

i No.	R^{61}	R^{62}	R^{63}	P_1	n	Yield	ESI-MS
i77	O-4-pyridyl	H	2-naphthyl	Boc	4	76%	$(M+H)^+$ = 609
i78	OPh	H	5,6,7,8-tetrahydro-naphthalen-2-yl	Boc	4	50%	$(M+H)^+$ = 612

Step E:

To the N-Boc-protected product of general procedure E, step D (20 mmol) in dichloromethane (180 ml) is added dropwise trifluoroacetic acid (180 mmol) and the mixture is stirred overnight. The yellow solution is added dropwise to sat. aq. sodium carbonate (190 mmol) and the mixture is stirred for another 30 min. The org. layer is separated, dried over sodium sulfate, and concentrated *in vacuo*. Flash chromatography (silica, dichloromethane / MeOH 20:1) gave final products of formula (Ia), see table I (examples 1 to 8).

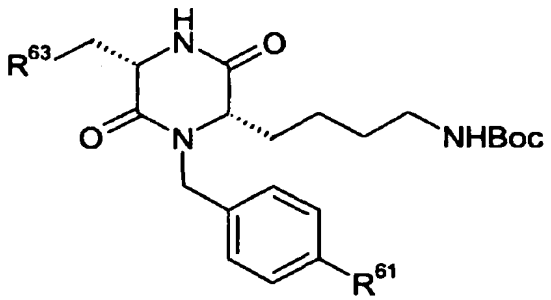
Step F:

To the O-TBDPS-protected product of general procedure F, step C (3.08 mmol) in THF (50 ml) is added N-ethyldiisopropylamine (6 mmol) followed by Boc anhydride (3.5 mmol) and the mixture is stirred at room temperature for 1 h. The org. layer is diluted with ethyl acetate (50 ml) and extracted with water (2x40 ml). The org. layer is separated and dried over sodium sulfate. Flash chromatography (silica, ethyl acetate/petroleum ether 3:1 → ethyl acetate) afforded the Boc-protected intermediate.

To the N-Boc-O-TBDPS-protected intermediate (2 mmol) in THF (20 ml) is added at room temperature tetrabutylammonium fluoride (1 N in THF, 8 mmol), followed by glacial acetic acid (0.5 ml) and the mixture is stirred for 2 h. Water (30 ml) is added, the aq. layer is extracted with ethyl acetate (3x50 ml), and the combined org. layers are dried over sodium sulfate. Flash chromatography (silica, dichloromethane/MeOH 25:1) gave the crude phenolic intermediate.

To the crude phenol (0.5 mmol), the corresponding boronic acid (1.5 mmol), copper(II) acetate (0.5 mmol), and molecular sieves (4 Å, powdered, 500 mg) in dichloromethane is added under argon at room temperature triethylamine (2.5 mmol) and the mixture is stirred overnight. Flash chromatography (silica, dichloromethane / MeOH 50:1 → 30:1) gave the product.

Examples of intermediates of the formula below prepared according to the general procedure E, step F, are shown below:



i No.	R^{61}	R^{63}	Yield	ESI-MS
i79	O-(2-Me-C_6H_4)	2-naphthyl	41%	$(M+H)^+$ = 622
i80	O-(3-Cl-C_6H_4)	2-naphthyl	72%	$(M+H)^+$ = 642

N-Boc-Deprotection is achieved according to procedure E, step E to give the final products of formula (Ib), see table III, examples 9 to 10.

Step G:

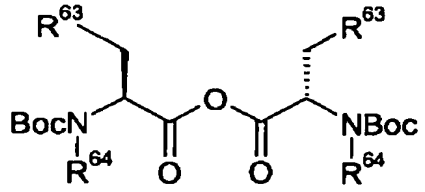
N-Cbz-protected compound of general procedure E, step D (20 mmol) in MeOH (150 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 90 min. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. Trituration (dichloro-methane/ether/petroleum ether) and drying under high vacuum yields the final products of general formula (Id), see table VI, examples 21 to 25.

General Procedure (F): Anhydride method

Step A:

To *N*-Boc-protected amino acid (20 mmol) in THF (150 ml) is added at room temperature N,N'-diisopropylcarbodiimide (10 mmol) and the mixture is stirred overnight. The mixture is concentrated *in vacuo* and the residue triturated (petroleum ether). The precipitate is collected by filtration and washed with petroleum ether and dried under high vacuum.

Examples of intermediate compounds of the formula below prepared according to the general procedure F, step F, are shown below:

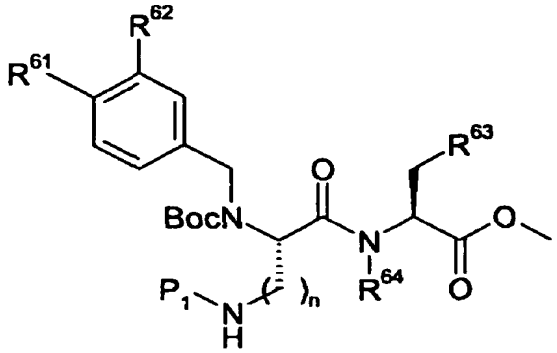


i No.	R^{63}	R^{64}	Yield
i81	2-naphthyl	H	90%
i82	2-naphthyl	Me	99%

Step B:

To the intermediate products from general procedure E, step A (2 mmol) and general procedure G, step A (4 mmol) in THF (60 ml) is added N-ethyldiisopropylamine (4.8 mmol) and the mixture is heated to reflux for 5 h and then stirred at room temperature overnight. The mixture is concentrated *in vacuo*, diluted with ethyl acetate (100 ml). The org. layer is washed with sat. aq. sodium bicarbonate, dried over sodium sulfate, and evaporated *in vacuo*. Flash chromatography (silica, ethyl acetate/petroleum ether 3:1 → 2:1) afforded the product.

Examples of intermediate compounds of the formula below prepared according to the general procedure F, step B, are shown below:



i No.	R^{61}	R^{62}	R^{63}	R^{64}	P1	n	Yield	ESI-MS
i83	Ph	H	2-naphthyl	H	Boc	4	78%	$(M+Na)^+$ = 746
i84	Ph	H	2-naphthyl	H	Cbz	4	crude	$(M+H)^+$ = 758
i85	Ph	H	2-naphthyl	Me	Cbz	4	crude	$(M+H)^+$ = 772
i86	OBn	H	2-naphthyl	H	Boc	4	81%	$(M+Na)^+$ = 776
i87	CH2Ph	H	2-naphthyl	H	Boc	4	25%	$(M+H)^+$ = 738
i88	N(Me)Ph	H	2-naphthyl	H	Boc	4	32%	$(M+H)^+$ = 753
i89	OCbz	H	2-naphthyl	H	Boc	4	37%	$(M+H)^+$ = 798
i90	OTBDPS	H	2-naphthyl	H	Boc	4	crude	$(M+H)^+$ = 902
i91	OPh	Me	2-naphthyl	H	Boc	4	crude	$(M+H)^+$ = 754
i92	OPh	OMe	2-naphthyl	H	Boc	4	crude	$(M+H)^+$ = 770
i93	Ph	H	2-naphthyl	H	Cbz	5	crude	$(M+H)^+$ = 772

Step C:

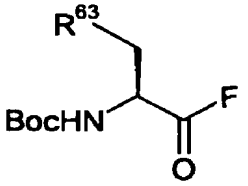
To the product of general procedure F, step B or the product of general procedure G, step B (2 mmol) in dichloromethane (50 ml) is added TFA (4.5 ml) and the mixture is stirred at room temperature for 3 h. The mixture is neutralized with sat. aq. sodium bicarbonate (250 ml) and the aq. layer is extracted with dichloromethane (4x150 ml). The combined org. layers are dried over sodium sulfate and evaporated *in vacuo* to give the final products of formula (Ic), see table IV, examples 11 to 20.

General Procedure (G): Acid fluoride method

Step A:

To *N*-Boc-protected amino acid (12 mmol) in dichloromethane (30 ml) is added at –15°C pyridine (12 mmol) followed by slow addition of cyanuric fluoride (60 mmol). The mixture is stirred for 1 h at –15°C, diluted with ice water (60 ml) and dichloromethane (100 ml), and the precipitation removed by filtration. The layers are separated and the aq. layer is extracted with dichloromethane (30 ml). The combined org. layers are washed with ice water (50 ml), dried over sodium sulfate, and evaporated *in vacuo* at 20°C to give the crude acid fluoride.

Examples of intermediate compounds of the formula below prepared according to the general procedure G, step A, are shown below:

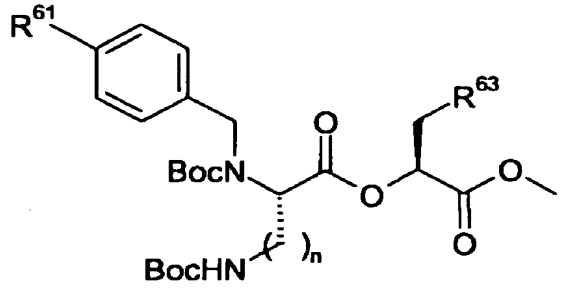


i No:	R^{63}	Yield
i94	2-naphthyl	91%, crude
i95	3-MeO-naphthalen-2-yl	quant., crude

Step B:

To the product of general procedure E, step A (4.5 mmol) and N-ethyldiisopropyl-amine (9 mmol) in dichloromethane (90 ml) is added at 0°C the product of general procedure G, step D (6.75 mmol) and the mixture is stirred at 0°C for 30 min., at room temperature for 2 h, and heated to refluxovernight. The mixture is diluted with dichloromethane (100 ml), the org. layer is washed with sat. aq. sodium bicarbonate, and dried over sodium sulfate. Flash chromatography (silica, ethyl acetate / petroleum ether 1:2) afforded the product.

Examples of intermediate compounds of the formula below prepared according to the general procedure G, step B, are shown below:



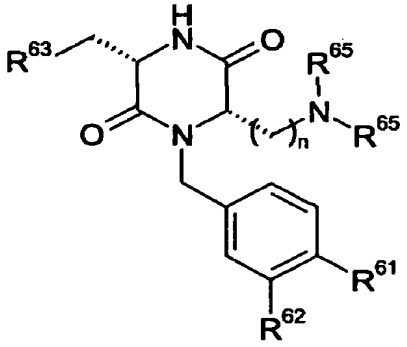
i No	R^{61}	R^{63}	n	Yield	ESI-MS
i96	OPh	2-naphthyl	4	61%	$(M+H)^+$ = 738
i97	OBn	2-naphthyl	4	28%	$(M+Na)^+$ = 776

i No	R^{61}	R^{63}	n	Yield	ESI-MS
i98	Ph	3-MeO-naphthalen-2-yl	4	crude	$(M+H)^+$ = 754

Step C:

To the product of general procedure E, step E-G (3 mmol) and aldehyde (12 mmol) in THF (120 ml) is added p-toluenesulfonic acid hydrate (3.6 mmol) and sodium triacetoxyborohydride (12.5 mmol) and the mixture is stirred at room temperature for 48 h. Sat. aq. sodium bicarbonate (100 ml) is added, the mixture is stirred for another 30 min., and then extracted with ether (3x100 ml). The combined org. layers are dried over sodium sulfate and concentrated *in vacuo*. Flash chromatography (silica, ethyl acetate) and trituration (ether / petroleum ether)afforded the product.

Examples of intermediate compounds of the formula below prepared according to the general procedure G, step C, are shown below:



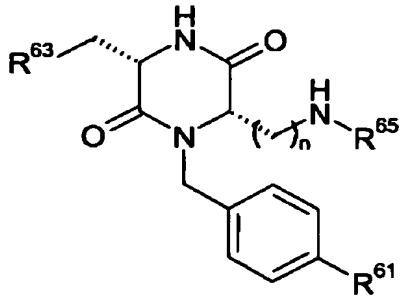
i No.	R^{61}	R^{62}	R^{63}	R^{65}	n	Yield	ESI-MS
i99	Ph	H	2-naphthyl	N-Cbz-piperidin-4-yl-methyl	1	96%	$(M+H)^+$=913
i100	OPh	H	2-naphthyl	N-Cbz-piperidin-4-yl-methyl	1	85%	$(M-H)^+$=928
i101	H	OPh	2-naphthyl	N-Cbz-piperidin-4-yl-methyl	1	93%	$(M+H)^+$=928
i102	OPh	H	2-naphthyl	3-(N-Cbz-amino)-propyl	1	60%	$(M+H)^+$=848
i103	OPh	H	2-naphthyl	1H-imidazol-4-yl-methyl	1	45%	$(M+H)^+$=610
i104	OPh	H	4-OCF_3-C_6H_4	N-Boc-piperidin-4-yl-methyl	1	59%	$(M+H)^+$=894
i105	OPh	H	4-OCF_2H-C_6H_4	N-Boc-piperidin-4-yl-methyl	1	74%	$(M+H)^+$=876
i106	OPh	H	4-CF_3-C_6H_4	N-Cbz-piperidin-4-yl-methyl	1	47%	$(M+H)^+$=946
i107	OPh	H	4-CF_3-C_6H_4	N-Boc-piperidin-4-yl-methyl	1	71%	$(M+H)^+$=878
i108	OPh	H	3,4-Cl_2-C_6H_3	N-Boc-piperidin-4-yl-methyl	1	82%	$(M+H)^+$=878
i109	OPh	H	2-naphthyl	N-Cbz-piperidin-4-yl-methyl	2	quant	$(M+H)^+$=942

Step D:

To the product of general procedure E, step E-G (4 mmol) and aldehyde (4 mmol) in THF (100 ml) is added p-toluenesulfonic acid hydrate (4 mmol) and sodium triacetoxyborohydride (8.3 mmol) and the mixture is stirred at room temperature for 2 h. Sat. aq. sodium bicarbonate (100 ml) is added, the mixture is stirred for another 30 min., and then extracted with ether (4x100 ml). The combined org. layers are dried over sodium sulfate and

concentrated *in vacuo*. Flash chromatography (silica, dichloromethane/MeOH 20:1) afforded the product.

Examples of intermediate compounds of the formula below prepared according to the general procedure G, step D, are shown below:



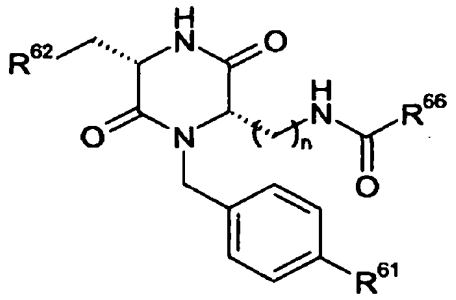
5

i No.	R^{61}	R^{63}	R^{65}	n	Yield	ESI-MS
i110	Ph	2-naphthyl	N-Cbz-piperidin-4-yl-methyl	1	81%	$(M+H)^+$=681
i111	OPh	2-naphthyl	N-Cbz-piperidin-4-yl-methyl	1	78%	$(M-H)^+$=697
i112	Ph	2-naphthyl	2-(N-Boc-amino)-ethyl	1	67%	$(M+H)^+$=593
i113	OPh	4-CF_3-C_6H_4	N-Cbz-piperidin-4-yl-methyl	1	62%	$(M+H)^+$=715
i114	OPh	4-OCF_3-3-Cl-C_6H_3	N-Cbz-piperidin-4-yl-methyl	1	42%	$(M+H)^+$=765
i115	OPh	3,4-Cl_2-C_6H_3	N-Boc-piperidin-4-yl-methyl	1	59%	$(M+H)^+$=681
i116	Ph	2-naphthyl	1H-imidazol-4-yl-methyl	1	crude	$(M+H)^+$=530
i117	Ph	2-naphthyl	N-Boc-piperidin-4-yl	1	45%	$(M+H)^+$=633
i118	Ph	2-naphthyl	4-(N-Boc-amino)-cyclohexyl	1	89%	$(M+H)^+$=647
i119	Ph	2-naphthyl	4-pyridyl-methyl	1	crude	$(M+H)^+$=541
i120	OPh	2-naphthyl	N-Cbz-piperidin-4-yl-methyl	2	crude	$(M+H)^+$=711

Step E: Acylation using free carboxylic acids

To the product of general procedure E, step E to G (0.6 mmol), the corresponding carboxylic acid (0.6 mmol), TBTU (0.615 mmol), and HOBt (0.615 mmol) in THF (15 ml) is added at room temperature N-ethyldiisopropylamine (2.1 mmol) and the mixture is stirred overnight. The mixture is diluted with ethyl acetate (100 ml), extracted with sat. aq. sodium bicarbonate (100 ml), and dried over sodium sulfate. Flash chromatography (silica, dichloromethane / MeOH 49:1 → 19:1) gave the product.

Examples of intermediate compounds of the formula below prepared according to the general procedure G, step E, are shown below:

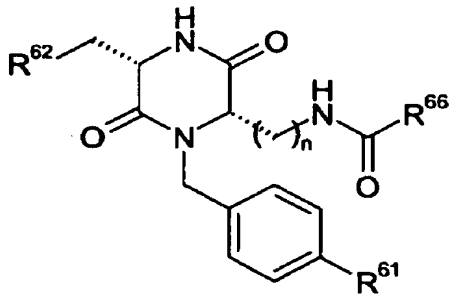


i No.	R^{61}	R^{62}	R^{66}	n	Yield	ESI-MS
i121	Ph	2-naphthyl	N,N-dimethyl-amino-methyl	1	25%	$(M+H)^+$=535
i122	Ph	2-naphthyl	3-(N,N-diethyl-amino)-ethyl	1	62%	$(M+H)^+$=577
i123	Ph	2-naphthyl	N-Boc-piperidin-4-yl	1	85%	$(M-H)^-$=659
i124	Ph	2-naphthyl	N-Boc-piperidin-3-yl	1	97%	$(M+H)^+$=661

Step F: Acylation using acid chlorides

To the product of general procedure E, step E to G or general procedure G, step C (0.7 mmol) and the corresponding acid chloride (0.77 mmol) in dichloromethane (20 ml) is added at room temperature N-ethyldiisopropylamine (2.1 mmol) and the mixture is stirred overnight. The mixture is diluted with dichloromethane (100 ml), extracted with sat. aq. sodium bicarbonate (100 ml), and dried over sodium sulfate. Flash chromatography (silica, dichloromethane / MeOH 49:1 → 19:1) gave the product.

Examples of intermediate compounds of the formula below prepared according to the general procedure G, step F, are shown below:

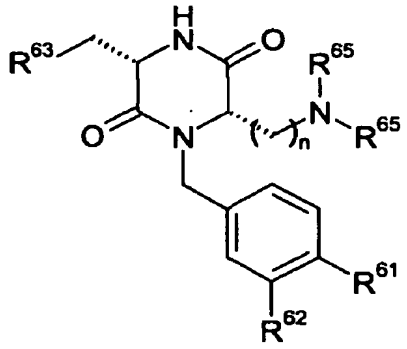


i No.	R^{61}	R^{63}	R^{68}	n	Yield	ESI-MS
i125	Ph	2-naphthyl	4-cyanophenyl	1	97%	$(M+H)^+$ = 579
i126	Ph	2-naphthyl	4-methyl-piperazyl	1	96%	$(M+H)^+$ = 576
i127	Ph	2-naphthyl	4-pyridyl	1	79%	$(M+H)^+$ = 555

Step G: Cbz-Deprotection

N-Cbz-Protected product from general procedure G, step C (3 mmol) in MeOH (150 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 90 min. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. Purification by HPLC (ZorbaxSB-C18 (5 µm) column, gradient of water / MeCN + 0.1% formic acid, detection at 254 nm and 230 nm) and lyophilization afforded the product.

Examples of intermediate compounds of the formula below prepared according to the general procedure G, step G, are shown below:

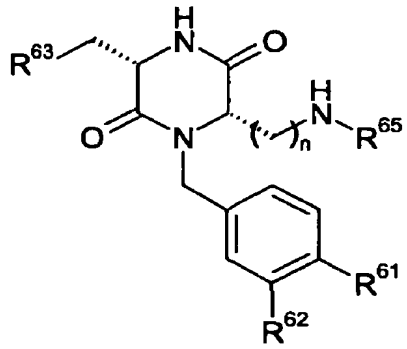


i No.	R^{61}	R^{62}	R^{63}	R^{65}	n	Yield	ESI-MS
i128	Ph	H	2-naphthyl	piperidin-4-yl-methyl	1	99%	$(M+H)^+$ = 644
i129	OPh	H	2-naphthyl	piperidin-4-yl-methyl	1	89%	$(M+H)^+$ = 660
i130	H	OPh	2-naphthyl	piperidin-4-yl-methyl	1	90%	$(M+H)^+$ = 660
i131	OPh	H	2-naphthyl	piperidin-4-yl-methyl	1	78%	$(M+H)^+$ = 580
i132	OPh	H	4-CF_3-C_6H_4	piperidin-4-yl-methyl	1	91%	$(M+H)^+$ = 678
i133	OPh	H	2-naphthyl	piperidin-4-yl-methyl	2	93%	$(M+H)^+$ = 674

Step H: Cbz-Deprotection

N-Cbz-Protected product from general procedure G, step D to F (3 mmol) in MeOH (150 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 90 min. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. Trituration (dichloromethane / ether / petroleum ether) and drying under high vacuum yielded the product.

Examples of intermediate compounds of the formula below prepared according to the general procedure G, step H, are shown below:



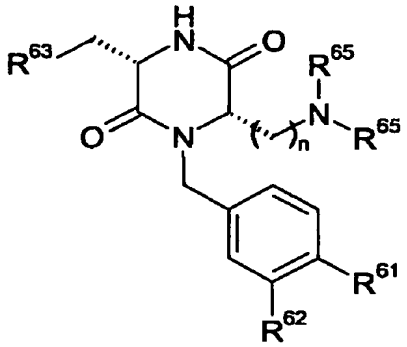
i No	R^{61}	R^{62}	R^{63}	R^{65}	n	Yield	ESI-MS
i134	Ph	H	2-naphthyl	piperidin-4-yl-methyl	1	75%	$(M+H)^+$ = 547

Step I: Boc-Deprotection

To the N-Boc-protected product of general procedure G, step C (2 mmol) in dichloromethane (18 ml) is added dropwise trifluoroacetic acid (18 mmol) and the mixture is stirred overnight. The yellow solution is added dropwise to sat. aq. sodium carbonate (19

mmol) and the mixture is stirred for another 30 min. The org. layer is separated, dried over sodium sulfate, and concentrated *in vacuo* Purification by HPLC (ZorbaxSB-C18 (5 µm) column, gradient of water / MeCN + 0.1% formic acid, detection at 254 nm and 230 nm) and lyophilization afforded the product.

Examples of intermediate compounds of the formula below prepared according to the general procedure G, step I, are shown below:

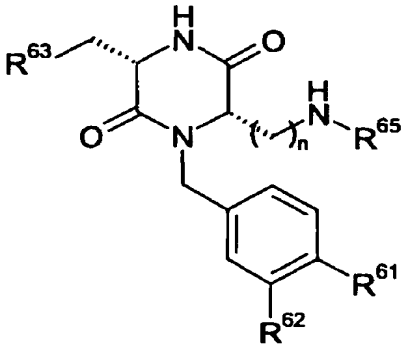


i No.	R^{61}	R^{62}	R^{63}	R^{65}	n	Yield	ESI-MS
i135	OPh	H	4-OCF_3-C_6H_4	piperidin-4-yl-methyl	1	quant.	$(M+H)^+$ = 694
i136	OPh	H	4-CF_2H-C_6H_4	piperidin-4-yl-methyl	1	59%	$(M+H)^+$ = 676
i137	OPh	H	3,4-Cl_2-C_6H_3	piperidin-4-yl-methyl	1	97%	$(M+H)^+$ = 679
i138	OPh	H	4-CF_3-C_6H_4	piperidin-4-yl-methyl	1	33%	$(M+H)^+$ = 678

Step J: Boc-Deprotection

To the N-Boc-protected product of general procedure G, step D to F (2 mmol) in dichloromethane (18 ml) is added dropwise trifluoroacetic acid (18 mmol) and the mixture is stirred overnight. The yellow solution is added dropwise to sat. aq. sodium carbonate (19 mmol) and the mixture is stirred for another 30 min. The org. layer is separated, dried over sodium sulfate, and concentrated *in vacuo*. Purification by HPLC (ZorbaxSB-C18 (5 µm) column, gradient of water/MeCN + 0.1% formic acid, detection at 254 nm and 230 nm) and lyophilization afforded the product.

Intermediate compounds prepared according to the general procedure G, step J:



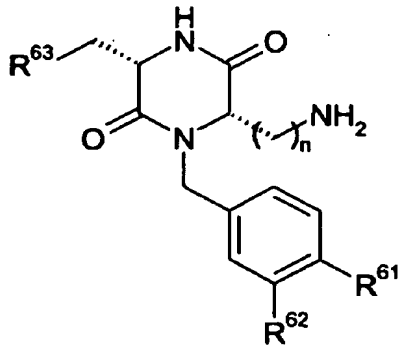
i No.	R^{61}	R^{62}	R^{63}	R^{65}	n	Yield	ESI-MS
i139	Ph	H	2-naphthyl	2-amino-ethyl	1	16%	$(M+H)^+$ = 493

i No.	R^{61}	R^{62}	R^{63}	R^{65}	n	Yield	ESI-MS
i140	Ph	H	2-naphthyl	piperidin-4-yl	1	52%	$(M+H)^+ = 533$
i141	Ph	H	2-naphthyl	4-amino-cyclo-hexyl	1	61%	$(M+H)^+ = 547$
i142	Ph	H	2-naphthyl	3-amino-propionyl	1	89%	$(M+H)^+ = 521$
i143	Ph	H	2-naphthyl	piperidin-4-yl-carbonyl	1	99%	$(M+H)^+ = 561$
i144	Ph	H	2-naphthyl	piperidin-3-yl-carbonyl	1	87%	$(M+H)^+ = 561$

Examples of compounds according to the present invention are shown below. These examples are provided for illustrative purposes only and shall not be construed as limiting the scope of the present invention as defined by the appended claims.

Examples 1 to 8

Intermediate compounds prepared according to the general procedure E, step E of the general formula (Ia) are shown in Table I, and compounds prepared according to the general procedure E, step E of the general formula (Ia) are shown in Table II



Formula (Ia)

The number of the intermediate used as starting compound in general procedure E, step E are stated under i No.

Table I

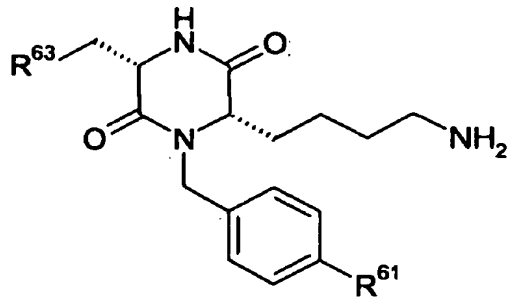
Intermediate no	i No.	R^{61}	R^{62}	R^{63}	n	Yield	ESI-MS $(M+H)^+$
i145	i58	Ph	H	2-naphthyl	1	93%	450
i146	i60	OPh	H	2-naphthyl	1	81%	466
i147	i61	H	OPh	2-naphthyl	1	90%	466
i148	i66	OPh	H	4-CF_3-C_6H_4	1	quant.	484
i149	i62	OPh	H	4-OCF_3-C_6H_4	1	98%	500
i150	i63	OPh	H	4-OCF_2H-C_6H_4	1	98%	482
i151	i64	OPh	H	4-CF_3-3-Cl-C_6H_3	1	89%	534
i152	i65	OPh	H	3,4-Cl_2-C_6H_3	1	93%	485
i153	i67	Ph	H	2-naphthyl	2	51%	464
i154	i68	OPh	H	2-naphthyl	2	57%	480

Table II

Example No	i No.	R^{61}	R^{62}	R^{63}	n	Yield	ESI-MS $(M+H)^+$
1	i70	Ph	H	2-naphthyl	4	60%	492
2	i74	OPh	H	4-MeO-3-Cl-C_6H_3	4	97%	522
3	i71	Ph	H	1-MeO-naphthalen-2-yl	4	48%	522
4	i72	Ph	H	6-Cl-naph-thalen-2-yl	4	30%	526
5	i75	OPh	H	4-NH_2-3,5-Br_2-C_6H_2	4	98%	629
6	i76	OPh	H	4-OH-3,5-Br_2-C_6H_2	4	99%	630
7	i77	O-4-pyridyl	H	2-naphthyl	4	70%	509
8	i78	OPh	H	5,6,7,8-tetrahydronaphthalen-2-yl	4	52%	512

Examples 9 to 10

Compounds prepared according to the general procedure E, step E of the general formula (Ib) are shown in Table III:



Formula (Ib)

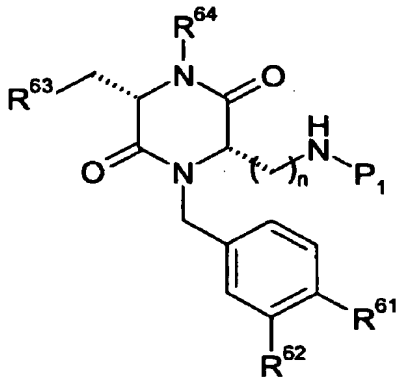
The number of the intermediate used as starting compound in general procedure E, step E are stated under i No.

Table III

Example no	i No.	R^{61}	R^{63}	Yield	ESI-MS $(M+H)^+$
9	i79	O-(2-Me-C_6H_4)	2-naphthyl	99%	522
10	i80	O-(3-Cl-C_6H_4)	2-naphthyl	81%	542

Examples 11 to 20

Intermediate compounds prepared according to the general procedure F, step C of general formula (Ic) are shown in Table IV, and compounds prepared according to the general procedure F, step C of general formula (Ic) are shown in Table V:



Formula (Ic)

The number of the intermediate used as starting compound in general procedure F, step C are stated under i No.

Table IV

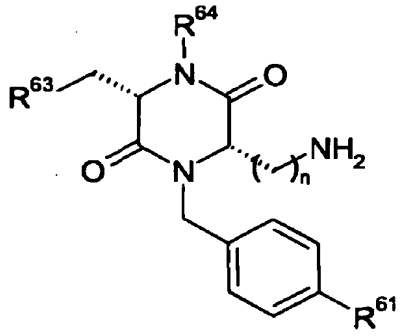
Intermediate no	i No.	R^{61}	R^{62}	R^{63}	R^{64}	P_1	n	Yield	ESI-MS $(M+H)^+$
i155	i84	Ph	H	2-naphthyl	H	Cbz	4	99%	626
i156	i85	Ph	H	2-naphthyl	Me	Cbz	4	99%	640
i157	i93	Ph	H	2-naphthyl	H	Cbz	5	99%	640

Table V

Example no	i No.	R^{61}	R^{62}	R^{63}	R^{64}	P_1	n	Yield	ESI-MS $(M+H)^+$
11	i83	Ph	H	2-naphthyl	H	H	4	97%	492
12	i98	Ph	H	3-MeO-naphthalen-2-yl	H	H	4	99%	522
13	i96	OPh	H	2-naphthyl	H	H	4	97%	508
14	i86	OBn	H	2-naphthyl	H	H	4	96%	522
15	i90	OTBDPS	H	2-naphthyl	H	H	4	quant.	670
16	i89	OCbz	H	2-naphthyl	H	H	4	99%	566
17	i88	N(Me)Ph	H	2-naphthyl	H	H	4	99%	521
18	i87	CH_2Ph	H	2-naphthyl	H	H	4	99%	506
19	i91	OPh	Me	2-naphthyl	H	H	4	99%	522
20	i92	OPh	OMe	2-naphthyl	H	H	4	99%	538

Examples 21 to 25

Compounds prepared according to the general procedure E, step G of the general formula (Id) are shown in Table VI:



Formula (Id)

The number of the intermediate used as starting compound in general procedure E, step G are stated under i No.

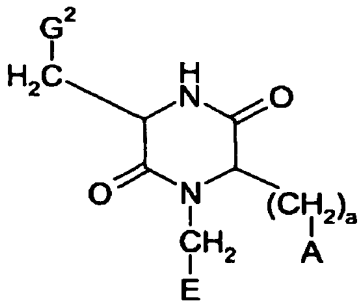
Table VI

Example no	i No.	R^{61}	R^{63}	R^{64}	n	Yield	ESI-MS $(M+H)^+$
21	i59	Ph	2-naphthyl	H	1	75%	450
22	i69	Ph	2-naphthyl	H	3	35%	478
23	i155	Ph	2-naphthyl	H	4	quant.	492
24	i156	Ph	2-naphthyl	Me	4	66%	506
25	i157	Ph	2-naphthyl	H	5	97%	506

Examples 26 and 27

Compounds of general formula (Ie) is synthesised on an ACT 440XT MOS robot according to general procedure A using as first building block (step A) Fmoc-D-Lys(Boc)-OH, Fmoc-D-Arg(Pbf)-OH, Fmoc-L-Lys(Boc)-OH or Fmoc L-Arg(Pbf)-OH. Benzaldehyde, 2-naphthylaldehyde, biphenyl-4-carbaldehyde or 4-benzyloxy-benzaldehyde is used as second building block (step C). The third building block (step D) is covered by Boc-D-Phe-OH, Boc-β-(2-naphthyl)-L-Ala-OH, Boc-D-Ser(Bzl)-OH, Boc-β-(2-naphthyl)-D-Ala-OH, Boc-L-Phe-OH, or Boc-L-Ser(Bzl)-OH. 24 random samples are analysed using HPLC-MS method B.

Examples of compounds prepared according to said procedure of the general formula (Ie) are shown in Table VII:



Formula (Ie)

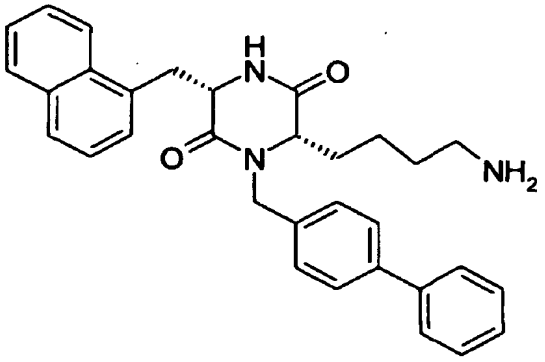
Table VII

Example No	a	A	E	G^2	Stereo pos 3	Stereo pos 6
26	4	$-NH_2$	-4-Biph	-2-Np	*S*	*S*
27	4	$-NH_2$	-Ph(4-OBzl)	-2-Np	*S*	*S*

Stereo pos 3 and 6 = Absolute stereochemistry at the position 3 and 6, respectively, of the diketopiperazin ring system

Example 28 (General procedure (B))

(*S,S*)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-naphthalen-1-ylmethyl-piperazine-2,5-dione



Step A:

30 mmol, 8.9 g H-Lys(Boc)-OMe hydrochloride, 1 equi., 5.5 g biphenyl-4-carbaldehyde and 1 equi., 5.1 ml DIPEA are suspended in 300 ml THF and the resulting mixture is stirred overnight. Then 2.9 equi., 5.4 g $NaCNBH_3$, 30 ml MeOH and 5 ml HOAc are added and the mixture is stirred for 7 h. The solvent is removed *in vacuo* and the residual oil is taken up in 300 ml ethyl acetate. The org. phase is washed once with 300 ml 1M NaOH. The aq. phase is extracted once with 300 ml ethyl acetate and the combined org. phases are

dried over sodium sulfate. The solvent is removed *in vacuo* and the crude product is used for the next step.

Step B:

20.0 mmol, 6.3 g Boc-1-Nal-OH is dissolved in 50 ml THF, 0.5 equi., 1.6 ml DIC is added and the resulting mixture is stirred for 20 min. Then 10 mmol of the crude product of step A is added in 100 ml THF and stirred overnight. Another 0.25 equi., 0.7 ml DIC is added and after 10 min 1 ml of DIPEA. The solvent is removed after 3 h of stirring and the residue is taken up in 100 ml ethyl acetate. The org. phase is washed with 100 ml 1 M HCl and twice with 100 ml 1M NaOH and dried over sodium sulfate. The solvent is removed *in vacuo* and the residual oil is purified on silica with ethyl acetate/heptane (1:1).

Step C:

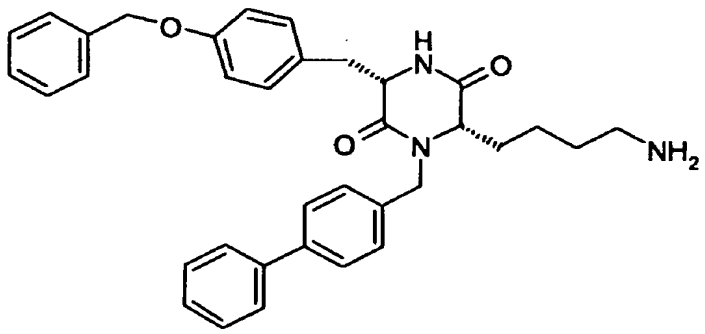
The purified product from step B is dissolved in 50 ml DCM and 50 ml TFA is added. The solvents are removed after 1 h. The residual oil is taken up in 50 ml DCM and 1 ml DIPEA is added. Another 1 ml of DIPEA is added after 1 h and again after an additional 90 min. The solvent is removed *in vacuo* and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

The product is freeze dried from 0.1 N HCl in water.

^{1}H NMR (400.13 MHz, DMSO-d_6): δ 0.69 (m, 3H), 1.22 (m, 3H), 2.43 (m, 2H), 3.47 (m, 1H), 3.61 (m, 2H), 4.10 (m, 1H), 4.45 (m, 1H), 4.94 (1H), 7.30 (m, 2H), 7.47 (m, 7H), 7.65 (m, 2H), 7.88 (m, 1H), 7.93 (m, 2H), 7.98 (m, 1H), 8.23 (m, 1H), 8.39 (m, 1H); HPLC-MS (Method C): *m/z* = 492 (M+1), 983 (2M+1); R_t = 3.43 min.

Example 29 (General procedure (B))

(*S,S*)-6-(4-Amino-butyl)-3-(4-benzyloxy-benzyl)-1-biphenyl-4-ylmethyl-piperazine-2,5-dione



Step A:

The intermediate from example **28**, Step A is used.

Step B:

20.0 mmol, 7.5 g Boc-1-Tyr(bzl)-OH is dissolved in 50 ml THF, 0.5 equi., 1.6 ml DIC is added and the resulting mixture is stirred for 40 min. Then 10 mmol of the crude product of step A is added in 50 ml THF. After 6 h 1.7 ml DIPEA is added and stirred overnight. The solvent is removed *in vacuo* and the residue is taken up in 100 ml ethyl acetate. The org. phase is washed twice with 100 ml 1 M HCl and twice with 100 ml sat. $NaHCO_3$ and dried over sodium sulfate. The solvent is removed *in vacuo* and the residual oil is purified on silica with ethyl acetate/heptane (2:3).

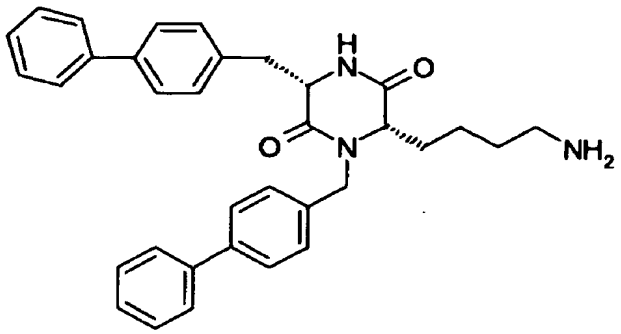
Step C:

The purified product from step B is dissolved in 100 ml DCM and 100 ml TFA is added. The solvents are removed *in vacuo* after 30 min. The residual oil is taken up in 100 ml DCM and 3 ml DIPEA is added. After 1 h the solvent is removed *in vacuo* and the oil is taken up in 100 ml DCM and 3 ml DIPEA. The solvent is removed *in vacuo* after 2 h and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

HPLC-MS (Method C): *m/z* = 548 (M+1); R_t = 3.23 min.

Example 30 (General procedure (B))

(S,S)-6-(4-Amino-butyl)-1,3-bis-biphenyl-4-ylmethyl-piperazine-2,5-dione



Step A:

The intermediate from example **28**, Step A is used.

Step B:

20.0 mmol, 6.8 g Boc-p-phenyl-Phe-OH is dissolved in 50 ml THF, 0.5 equi., 1.6 ml DIC is added and the resulting mixture is stirred for 30 min. Then 10 mmol of the crude product of step A is added in 50 ml THF. After 4.5 h 1.7 ml DIPEA is added and the mixture is stirred overnight. The solvent is removed *in vacuo* and the residue is taken up in 100 ml

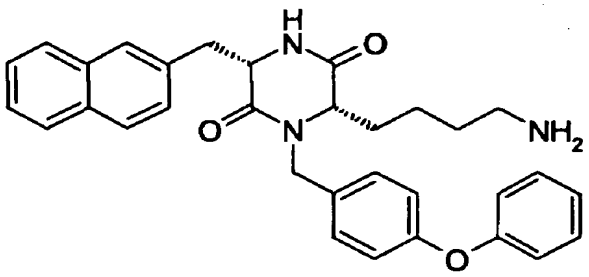
ethyl acetate. The org. phase is washed twice with 100 ml 1 M HCl and twice with 100 ml sat. $NaHCO_3$ and dried over sodium sulfate. The solvent is removed *in vacuo* and the residual oil is purified on silica with ethyl acetate/heptane (2:3).

Step C:

The purified product from step B is dissolved in 80 ml DCM and 80 ml TFA is added. The solvents are removed *in vacuo* after 70 min. The residual oil is taken up in 100 ml DCM and 1.8 ml DIPEA is added. After 1 h 1 ml DIPEA is added. The solvent is removed *in vacuo* after 3 h. The oil is again taken up in 100 ml DCM and 2 ml DIPEA are added. The solvent is removed *in vacuo* after stirring for 1.5 h and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.
HPLC-MS (Method C): *m/z* = 518 (M+1); R_t = 3.14 min.

Example 31

(*S,S*)-6-(4-Amino-butyl)-3-naphthalen-2-ylmethyl-1-(4-phenoxy-benzyl)-piperazine-2,5-dione



Step A:

2-*tert*-Butoxycarbonylamino-3-(2-naphtyl)propionic acid (5.00 g, 15.85 mmol) is dissolved in 100 ml of tetrahydrofuran in a 500 ml flask equipped with a magnetic stirrer. O-(1H-Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (6.31 g, 16.64 mmol), 1-hydroxybezotriazole (2.43 g, 15.85 mmol) and N-ethyldiisopropylamin (3.80 ml, 22.19 mmol) are added, and the mixture is stirred for 30 min, after which 20 ml of methanol is added. Stirred overnight at room temperature to give a clear yellow solution. Evaporated to a crude mixture, which is taken up in 150 ml of ethyl acetate and washed with 25 ml of aqueous sodium hydrogen sulfate (10%), 25 ml of aqueous sodium hydrogen carbonate (saturated), 25 ml of water, and 25 ml of brine, dried over magnesium sulfate and filtered. Concentrated *in vacuo* to give a crude oil, which is purified by flash chromatography (150 g of SiO_2, heptane:ethyl acetate (8:2)) to afford 5.52 g (quantitative yield) of (2S)-2-*tert*-butoxycarbonylamino-3-(2-naphthyl)propionic acid methyl ester as a yellow crystalline oil.
HPLC-MS: Rt = 6.57 min., (M+1) = 330, %Area by ELS = 100

Step B:

(2S)-2-*tert*-Butoxycarbonylamino-3-(2-naphthyl)propionic acid methyl ester (5.52 g, theoretically 15.85 mmol) is dissolved in 20 ml of ethyl acetate in a 500 ml flask equipped with a magnetic stirrer. To the stirred solution is added 80 ml of 2.8 M hydrogen chloride in ethyl acetate and the reaction is stirred for 2.5 hours under nitrogen. The clear mixture is concentrated *in vacuo* to give a solid, which is taken up in ethyl acetate, stirred for 10 min and filtered. The solid is dried *in vacuo* at 40 °C to give 3.91 g (93%) of (2S)-2-Amino-3-(2-naphthyl)propionic acid methyl ester hydrochloride as a white solid.

HPLC-MS: Rt = 3.70 min., (M+1) = 230, %Area by ELS = 100

Step C:

2-*tert*-Butoxycarbonylamino-6-(9H-fluoren-9-ylmethoxycarbonylamino)hexanoic acid (4.87 g, 10.39 mmol) is dissolved in 60 ml of dimethylformamide in a 250 ml flask equipped with a magnetic stirrer. 1-Hydroxybezotriazole (1.59 g, 10.39 mmol) and N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride (1.99 g, 10.39 mmol) are added and the mixture is stirred for 30 min, after which (2S)-2-amino-3-(2-naphthyl)propionic acid methyl ester (2.76 g, 10.39 mmol) and N-ethyldiisopropylamin (3.6 ml, 20.78 mmol) are added. Stirred for 3 days to give a clear orange solution. The reaction is added to 200 ml of ethyl acetate and washed with a mixture of 25 ml of water and 25 ml of aqueous sodium hydrogen carbonate (saturated). The aqueous phase is extracted with 100 ml of ethyl acetate. The combined organic phases are then washed with 50 ml of aqueous sodium hydrogen sulfate (10%), 50 ml of brine, dried over magnesium sulfate and filtered. This solution of (2S)-2-[2-*tert*-butoxycarbonylamino-6-(9H-fluoren-9-ylmethoxycarbonylamino) hexanoyl amino]-(2S)-3-(2-naphthyl)propionic acid methyl ester is used directly in the next step without further purification.

HPLC-MS: Rt = 7.73 min., (M+1) = 680, %Area by ELS = 99

Step D:

To (2S)-2-[2-*tert*-butoxycarbonylamino-6-(9H-fluoren-9-ylmethoxycarbonylamino)hexanoylamino]-(2S)-3-(2-naphthyl)propionic acid methyl ester (theoretically 10.39 mmol in 250 ml of ethyl acetate) is added 250 ml of 2.8 M hydrogen chloride in ethyl acetate. The reaction is stirred for 2 hours under nitrogen. Concentrated *in vacuo* to afford 5.86 g (92%) of (2S)-2-[2-amino-6-(9H-fluoren-9-ylmethoxycarbonylamino) hexanoylamino]-(2S)-3-(2-naphthyl)propionic acid methyl ester hydrochloride as orange oil.

HPLC-MS: Rt = 5.43 min., (M+1) = 580, %Area by ELS = 74

Step E:

To a solution of 2S)-2-[2-amino-6-(9H-fluoren-9-ylmethoxycarbonylamino)hexanoylamino]-(2S)-3-(2-naphthyl)propionic acid methyl ester (0.50 g, 0.81 mmol) in a mixture of 5 ml of tetrahydrofuran and 5 ml of methanol is added sodium acetate (0.27 g, 3.24 mmol), 4-phenoxybenzaldehyde (0.14 ml, 0.81 mmol), molecular sieves (4Å) and 1.0 M sodium cyanoborohydride (0.81 ml, 0.81 mmol) in tetrahydrofuran. Stirred overnight and then filtered through Hyflo Super Cel®. Concentrated *in vacuo* to afford (2S)-2-[6-(9H-fluoren-9-ylmethoxycarbonylamino)-2-(4-phenoxybenzylamino)hexanoylamino]-(2S)-3-(2-naphthyl)-propionic acid methyl ester (theoretically 0.81 mmol) as a solid, which is used without further purification.

HPLC-MS: Rt = 7.53 min., (M+1) = 762, %Area by ELS = 100

Step F:

A solution of (2S)-2-[6-(9H-fluoren-9-ylmethoxycarbonylamino)-2-(4-phenoxybenzylamino)-hexanoylamino]-(2S)-3-(2-naphthyl)propionic acid methyl ester (theoretically 0.81 mmol) in 15 ml of toluene, 15 ml of 1-butanol and 3 ml of acetic acid is stirred for 12 hours at 100 °C in a 250 ml flask equipped with a condenser. Concentrated *in vacuo*, dissolved in 100 ml of dichloromethane and washed with 20 ml of aqueous sodium hydrogen carbonate (saturated), 20 ml of aqueous sodium hydrogen sulfate (10%), 20 ml of brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford {(2S,5S)-4-[5-(2-naphthyl)methyl-3,6-dioxo-1-(4-phenoxybenzyl)piperazin-2-yl]butyl}carbamic acid (9H-fluoren-9-ylmethyl) ester (theoretically 0.81 mmol) as an oil. Used without further purification.

HPLC-MS: Rt = 8.28 min., (M+1) = 730, %Area by ELS = 100

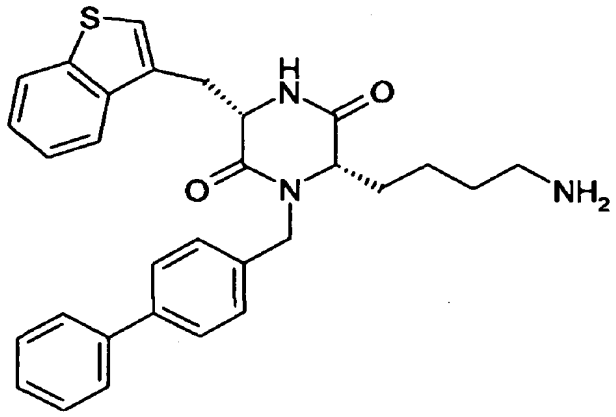
Step G:

To a solution of {(2S,5S)-4-[5-(2-naphthyl)methyl-3,6-dioxo-1-(4-phenoxybenzyl) piperazin-2-yl]butyl}carbamic acid (9H-fluoren-9-ylmethyl) ester (theoretically 0.81 mmol) in 10 ml of dichloromethane is added 10 ml of tris(2-aminoethyl)amine. Stirred for 2 hours under nitrogen. The reaction is added to 100 ml of dichloromethane and washed with 30 ml of brine, 3x50 ml of aqueous phosphate buffer (pH 6.6), 50 ml of brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford a crude oil which is purified by preparative HPLC (20-40% CH_3CN in water/0.1% trifluoroacetic acid, 40 min). The obtained pure fractions are combined and 1 ml of 1N aqueous hydrogen chloride is added. The compound is lyophilized to give 60.1 mg (14%) of the title compound as a hydrochloride-salt.

HPLC (A1): Rt = 33.22 min., 100 % (214 nm); HPLC (B1): Rt = 35.14 min., 100 % (214 nm);HPLC-MS: Rt = 4.83 min., (M+1) = 508, %Area by ELS = 100

Example 32 (General procedure (B))

(*S,S*)-6-(4-Amino-butyl)-3-benzo[b]thiophen-3-ylmethyl-1-biphenyl-4-ylmethyl-piperazine-2,5-dione



Step A:

The intermediate from example **28**, Step A is used.

Step B:

10.0 mmol, 3.21 g Boc-*β*-(3-benzothienyl)-Ala-OH is dissolved in 30 ml THF, 0.5 equi., 775 µl DIC is added and the resulting mixture is stirred for 30 min. Then 5 mmol of the crude product of step A is added in 30 ml THF. After 2.5 h 855 µl DIPEA is added and the mixture is stirred overnight. The solvent is removed *in vacuo* and the residue is taken up in 100 ml ethyl acetate. The org. phase is washed twice with 50 ml 1 M HCl and twice with 50 ml sat. $NaHCO_3$ and dried over sodium sulfate. The solvent is removed *in vacuo* and the residual oil is purified on silica with ethyl acetate/heptane (1:2).

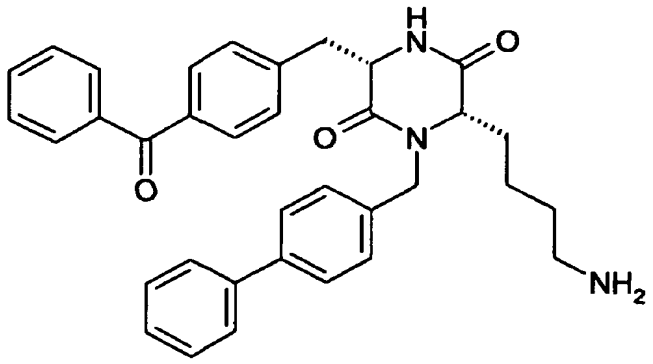
Step C:

The purified product from step B is dissolved in 50 ml DCM and 50 ml TFA is added. The solvents are removed *in vacuo* after 40 min. The residual oil is taken up in 50 ml DCM and 2.0 ml DIPEA is added. The solvent is removed *in vacuo* after 3 h. The oil is again taken up in 50 ml DCM and 1.5 ml DIPEA are added. The solvent is removed *in vacuo* after stirring for 1.5 h and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

HPLC-MS (Method C): *m/z* = 498 (M+1); R_t = 2.86 min.

Example 33 (General procedure (B))

(*S,S*)-6-(4-Amino-butyl)-3-(4-benzoyl-benzyl)-1-biphenyl-4-ylmethyl-piperazine-2,5-dione



Step A:

The intermediate from example **28**, Step A is used.

Step B:

10.0 mmol, 3.7 g Boc-p-Bz-Phe-OH is dissolved in 30 ml THF, 0.5 equi., 755 µl DIC is added and the resulting mixture is stirred for 30 min. Then 5 mmol of the crude product of step A is added in 30 ml THF. After 2.5 h 855 µl DIPEA is added and the mixture is stirred overnight. The solvent is removed *in vacuo* and the residue is taken up in 70 ml ethyl acetate. The org. phase is washed twice with 50 ml 1 M HCl and twice with 50 ml sat. $NaHCO_3$ and dried over sodium sulfate. The solvent is removed *in vacuo* and the residual oil is purified on silica with ethyl acetate/heptane (2:3).

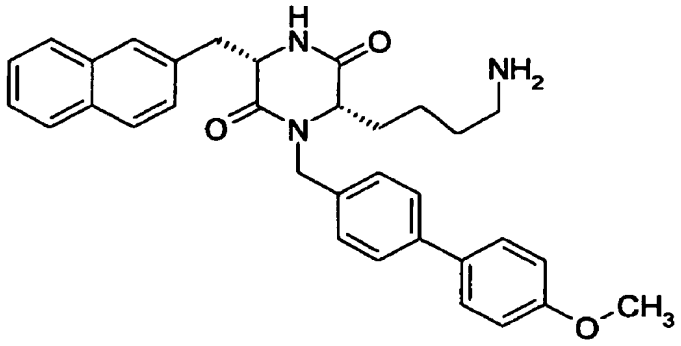
Step C:

The purified product from step B is dissolved in 50 ml DCM and 50 ml TFA is added. The solvents are removed *in vacuo* after 45 min. The residual oil is taken up in 50 ml DCM and 3.0 ml DIPEA is added. The solvent is removed *in vacuo* after 2.3 h and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

HPLC-MS (Method C): *m/z* = 546 (M+1); R_t = 2.98 min.

Example 34

(*S,S*)-6-(4-Amino-butyl)-1-(4'-methoxy-biphenyl-4-ylmethyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



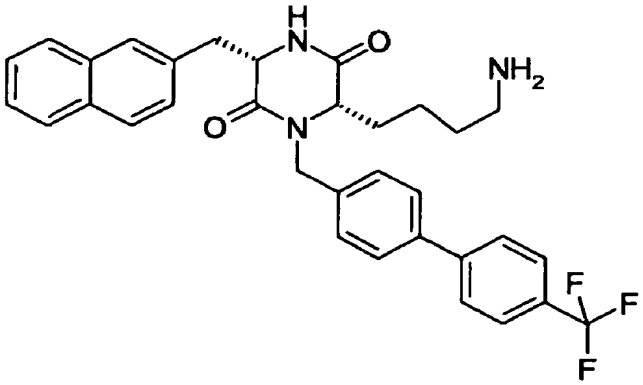
35 mg of the title compound is synthesized as described for example **31** using 4'-methoxy-biphenyl-4-carbaldehyde instead of 4-phenoxybenzaldehyde.

The title compound is purified by Sep-Pak® using 70 % acetonitrile in water/0.1 M hydrogen chloride as a mobile phase. The mobile phase is removed by lyophilization.

HPLC (A): Rt = 32.92 min., 90 % (214 nm); HPLC (B): Rt = 34.51 min., 89 % (214 nm);HPLC-MS: Rt = 4.67 min., (M+1) = 522, %Area by ELS = 97

Example 35

(*S,S*)-6-(4-Amino-butyl)-3-naphthalen-2-ylmethyl-1-(4'-trifluoromethyl-biphenyl-4-ylmethyl)-piperazine-2,5-dione



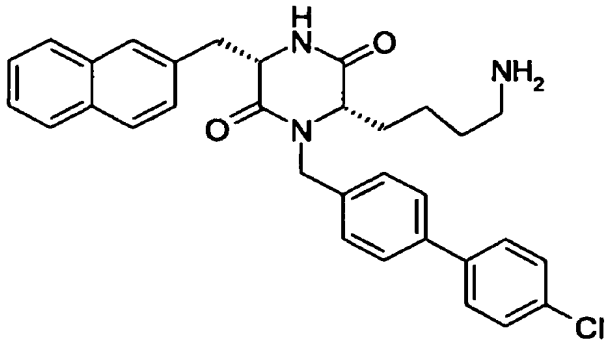
24 mg of the title compound is synthesized as described for example **31** using 4'-trifluoromethyl-biphenyl-4-carbaldehyde instead of 4-phenoxybenzaldehyde.

The title compound is purified by Sep-Pak® using 70 % acetonitrile in water/0,1 M hydrogen chloride as a mobile phase. The mobile phase is removed by lyophilization.

HPLC (A1): Rt = 38.26 min., 94 % (214 nm); HPLC (B1): Rt = 40.39 min., 94 % (214 nm);HPLC-MS: Rt = 5.22 min, (M+1) = 560, %Area by ELS = 100.

Example 36

(*S,S*)-6-(4-Amino-butyl)-1-(4'-chloro-biphenyl-4-ylmethyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



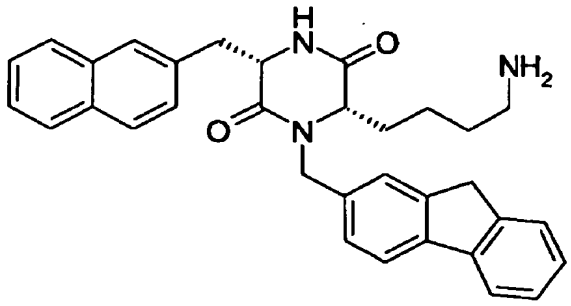
35 mg of the title compound is synthesized as described for example **31** using 4'-chloro-biphenyl-4-carbaldehyde instead of 4-phenoxybenzaldehyde.

The title compound is purified by Sep-Pak® using 70 % acetonitrile in water /0,1 M hydrogen chloride as a mobile phase. The mobile phase is removed by lyophilization.

HPLC (A1): Rt = 38.93 min., 87 % (214 nm); HPLC (B1): Rt = 38.64 min., 90 % (214 nm); HPLC-MS: Rt = 4.88 min, (M+1) = 526, %Area by ELS = 70.

Example 37

(*S,S*)-6-(4-Amino-butyl)-1-(9*H*-fluoren-2-ylmethyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



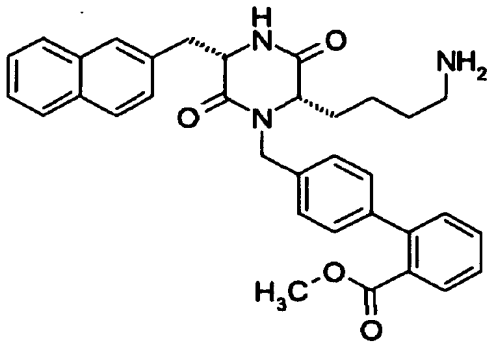
16.6 mg of the title compound is synthesized as described for example **31** using 9*H*-fluorene-carbaldehyde instead of 4-phenoxybenzaldehyde.

The title compound is purified by preparative HPLC (25-45% acetonitrile in water /0.1% trifluoroacetic acid, 40 min). The obtained pure fractions are combined and 1N aqueous

hydrogen chloride is added. The mobile phase is removed by lyophilization.
HPLC (A1): Rt = 33.34 min., 98% (214 nm); HPLC (B1): Rt = 35.38 min., 98 % (214 nm);
HPLC-MS: Rt = 4.93 min, (M+1) = 504, %Area by ELS = 66

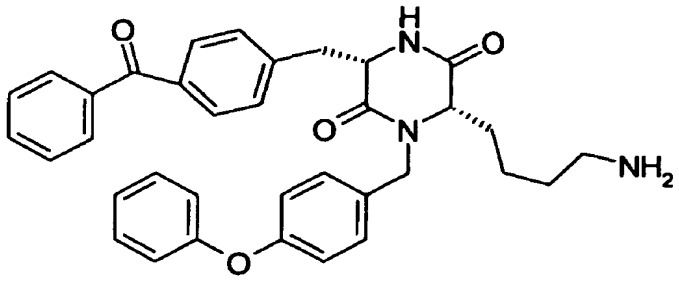
Example 38

(*S,S*)-4'-[2-(4-Amino-butyl)-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-ylmethyl]-biphenyl-2-carboxylic acid methyl



10.5 mg of the title compound is synthesized as described for example **31** using 9*H*-fluorene-carbaldehyde instead of 4-phenoxybenzaldehyde.
The title compound is purified by preparative HPLC (23-43% acetonitrile in water /0.1% trifluoroacetic acid, 40 min). The obtained pure fractions are combined and 1N aqueous hydrogen chloride is added. The mobile phase is removed by lyophilization.
HPLC (A1): Rt = 33.03 min., 100 % (214 nm); HPLC (B1): Rt = 34.98 min., 100 % (214 nm);
HPLC-MS: Rt = 4.42 min, (M+1) = 550, %Area by ELS = 100

Example 39 (General procedure (B))
(*S,S*)-6-(4-Amino-butyl)-3-(4-benzoyl-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione



Step A:

20 mmol, 5.9 g H-Lys(Boc)-OMe hydrochloride, 1 equi., 3.6 ml 4-phenoxy benzaldehyde and 1 equi., 3.5 ml DIPEA are suspended in 200 ml THF and the resulting

mixture is stirred overnight. Then 2.9 equi., 3.7 g $NaCNBH_3$, 20 ml MeOH and 10 ml HOAc are added and the mixture is stirred for 3 h. The solvent is removed *in vacuo* and the residual oil is taken up in 200 ml ethyl acetate. The org. phase is washed twice with 100 ml 1M NaOH. and dried over sodium sulfate. The solvent is removed *in vacuo* and the crude product is used for the next step.

Step B:

5.0 mmol, 1.9 g Boc-p-Bz-Phe-OH is dissolved in 15 ml THF, 0.5 equi. and 390 µl DIC is added and the resulting mixture is stirred for 30 min. Then 2.5 mmol of the crude product of step A is added in 15 ml THF. After 2.5 h 430 µl DIPEA is added and the mixture is stirred overnight. The solvent is removed *in vacuo* and the residue is taken up in 40 ml ethyl acetate. The org. phase is washed twice with 30 ml 1 M HCl and twice with 30 ml sat. $NaHCO_3$ and dried over sodium sulfate. The solvent is removed *in vacuo* and the residual oil is purified on silica with ethyl acetate/heptane (2:3).

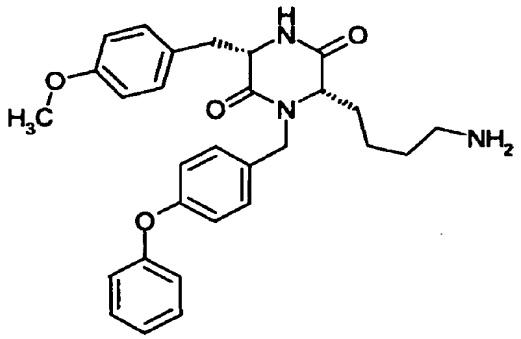
Step C:

The purified product from step B is dissolved in 30 ml DCM and 30 ml TFA is added. The solvents are removed *in vacuo* after 30 min. The residual oil is taken up in 30 ml DCM and 2.0 ml DIPEA is added. The solvent is removed *in vacuo* after 2 h and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

HPLC-MS (Method C): *m/z* = 562 (M+1); R_t = 3.02 min.

Example 40 (General procedure (B))

(*S,S*)-6-(4-Amino-butyl)-3-(4-methoxy-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione



Step A:

The intermediate from example **39**, Step A is used.

Step B:

5.0 mmol, 1.5 g Boc-p-methoxy-Phe-OH is dissolved in 15 ml THF, 0.5 equi., 390 µl DIC is added and the resulting mixture is stirred for 30 min. Then 2.5 mmol of the crude product of step A is added in 15 ml THF. After 3.5 h 430 µl DIPEA is added and the mixture is stirred overnight. The solvent is removed *in vacuo* and the residue is taken up in 40 ml ethyl acetate. The org. phase is washed twice with 25 ml 1 M HCl and twice with 25 ml sat. $NaHCO_3$ and dried over sodium sulfate. The solvent is removed *in vacuo* and the residual oil is purified on silica with ethyl acetate/heptane (2:3).

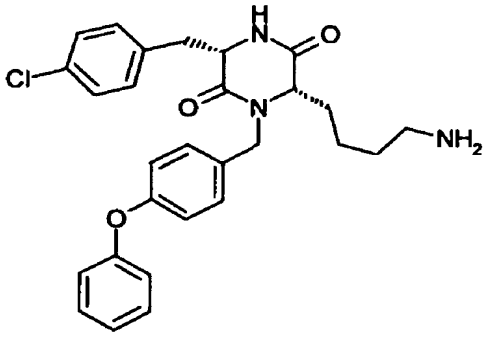
Step C:

The purified product from step B is dissolved in 30 ml DCM and 30 ml TFA is added. The solvents are removed *in vacuo* after 30 min. The residual oil is taken up in 30 ml DCM and 2.0 ml DIPEA is added. The solvent is removed *in vacuo* after 2.3 h and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

HPLC-MS (Method C): *m/z* = 488 (M+1); R_t = 2.92 min.

Example 41 (General procedure (B))

(*S,S*)-6-(4-Amino-butyl)-3-(4-chloro-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione



Step A:

The intermediate from example **39**, Step A is used.

Step B:

5.0 mmol, 1.5 g Boc-p-chloro-Phe-OH is dissolved in 15 ml THF, 0.5 equi., 390 µl DIC is added and the resulting mixture is stirred for 30 min. Then 2.5 mmol of the crude product of step A is added in 15 ml THF. After 2.5 h 430 µl DIPEA is added and the mixture is stirred overnight. The solvent is removed *in vacuo* and the residue is taken up in 40 ml ethyl acetate. The org. phase is washed twice with 25 ml 1 M HCl and twice with 25 ml sat.

$NaHCO_3$ and dried over sodium sulfate. The solvent is removed *in vacuo* and the residual oil is purified on silica with ethyl acetate/heptane (2:3).

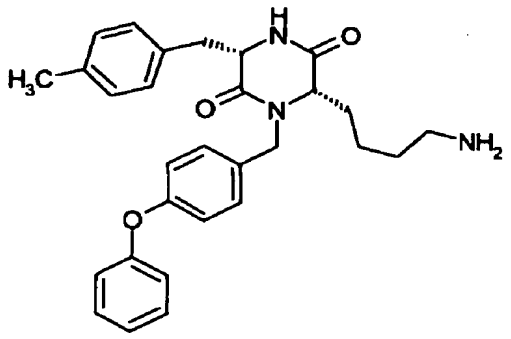
Step C:

The purified product from step B is dissolved in 25 ml DCM and 25 ml TFA is added. The solvents are removed *in vacuo* after 30 min. The residual oil is taken up in 40 ml DCM and 2.0 ml DIPEA is added. The solvent is removed *in vacuo* after 1.5 h and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

HPLC-MS (Method C): m/z = 492 (M+1); R_t = 2.75 min.

Example 42 (General procedure (B))

(*S,S*)-6-(4-Amino-butyl)-3-(4-methyl-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione



Step A:

The intermediate from example **39**, Step A is used.

Step B:

5.0 mmol, 1.4 g Boc-p-chloro-Phe-OH is dissolved in 15 ml THF, 0.5 equi., 390 µl DIC is added and the resulting mixture is stirred for 30 min. Then 2.5 mmol of the crude product of step A is added in 15 ml THF. After 2 h 430 µl DIPEA is added and the mixture is stirred overnight. The solvent is removed *in vacuo* and the residue is taken up in 40 ml ethyl acetate. The org. phase is washed twice with 25 ml 1 M HCl and twice with 25 ml sat. $NaHCO_3$ and dried over sodium sulfate. The solvent is removed *in vacuo* and the residual oil is purified on silica with ethyl acetate/heptane (2:3).

Step C:

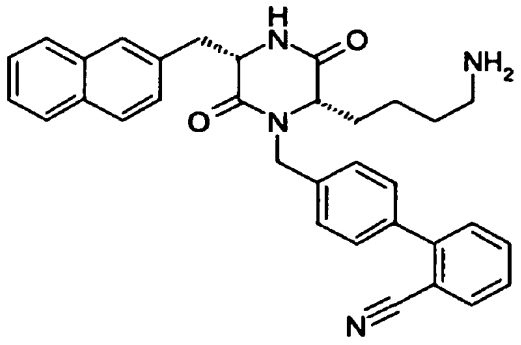
The purified product from step B is dissolved in 25 ml DCM and 25 ml TFA is added. The solvents are removed *in vacuo* after 30 min. The residual oil is taken up in 25 ml DCM and 2.0 ml DIPEA is added. The solvent is removed *in vacuo* after 1 h and the product is purified

on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

HPLC-MS (Method C): *m/z* = 472 (M+1); R_t = 2.80 min.

Example 43

(*S,S*)-4'-[2-(4-Amino-butyl)-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-ylmethyl]-biphenyl-2-carbonitrile



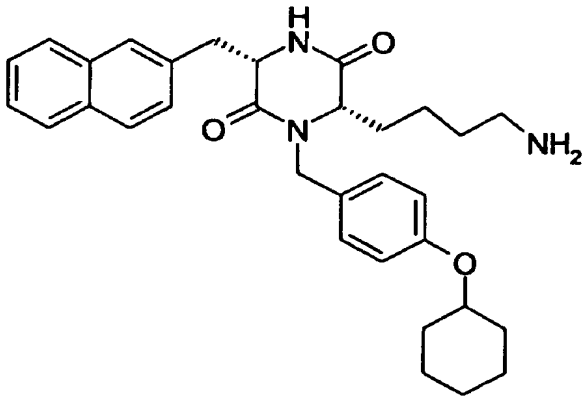
26 mg of the title compound is synthesized as described for example **31** using 4'-formyl-biphenyl-2-carbonitrile instead of 4-phenoxybenzaldehyde.

The title compound is purified by preparative HPLC (23-43% acetonitrile in water /0.1% trifluoroacetic acid, 40 min). The obtained pure fractions are combined and 1N aqueous hydrogen chloride is added. The mobile phase is removed by lyophilization.

HPLC-MS: R_t = 4.32 min, (M+1) = 517, %Area by ELS = 100

Example 44

(*S,S*)-6-(4-Amino-butyl)-1-(4-cyclohexyloxy-benzyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



Step A:

To a solution of H-Lys(Boc)-OMe HCl (3.0 g, 10 mmol) in THF (120 ml) is added 4-hydroxy-benzaldehyde (1.23 g, 10 mmol) and *N,N*-diisopropylethylamine (1.76 ml, 10 mmol), and the mixture is stirred for 5 h at room temperature. Then methanol (10 ml), acetic acid (4.8 ml) and sodium cyanoborohydride (1.9 g, 30 mmol) is added and the mixture is stirred overnight at room temperature. Then the mixture is evaporated *in vacuo* and the residue is taken up in ethyl acetate (150 ml) and filtered. The filtrate is washed with 1N sodium hydroxide (75 ml). The aqueous phase is extracted with ethyl acetate (75 ml) and the combined organic phases are dried over sodium sulfate and evaporated to dryness to give the crude product, which is used in the next step without further purification.

HPLC-MS (Method C): *m/z* = 367 (M+1); R_t = 2.23 min.

Step B:

To a solution of Boc-β-2-naphthyl-Ala-OH (4.4 g, 14 mmol) in THF (30 ml) is added *N,N'*-diisopropylcarbodiimide (1.1 ml, 7.1 mmol) and the mixture is stirred for 30 min at room temperature. A solution of crude product from step A (2.60 g, 7.1 mmol) in THF (20 ml) is added and the mixture is stirred for 7 h at room temperature. Then triethylamine (2.0 ml, 14 mmol) is added and stirring is continued overnight. The mixture is evaporated *in vacuo* and the residue is taken up in ethyl acetate (75 ml) and washed successively with 1 N HCl (50 ml) and saturated aqueous sodium hydrogen carbonate (50 ml), dried over sodium sulfate and evaporated to dryness. Column chromatography on silica (ethyl acetate/heptane (1:3 to 1:1)) afforded the intermediate in a yield of 2.4 g (50%).

HPLC-MS (Method C): *m/z* = 686 (M+23); R_t = 5.14 min.

Step C:

Triphenylphosphine (356 mg, 1.4 mmol) and cyclohexanol (136 mg, 1.4 mmol) is added to a solution of the product from step B (300 mg, 0.45 mmol) in THF (20 ml) with stirring at room temperature under nitrogen. A solution of diethyl azodicarboxylate (214 ml, 1.4 mmol) in THF (5 ml) is added dropwise during 30 min while the temperature is kept below 30 °C with cooling on an ice-bath. After stirring at room temperature for about 3 days the mixture is evaporated to dryness and purified on silica with ethyl acetate/heptane (1:3) affording a crude product, which is used in the next step without further purification.

Step D:

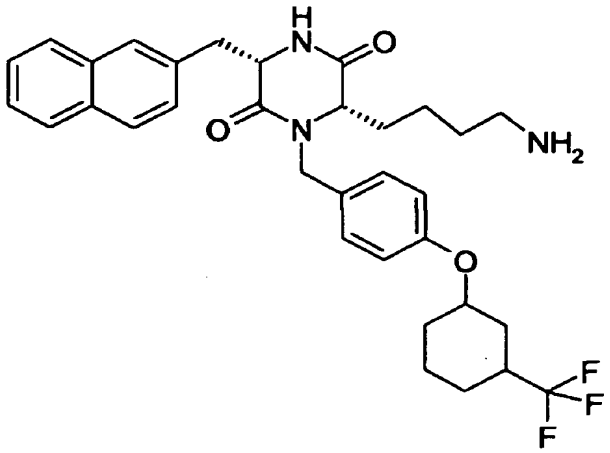
The product from step C (50 mg, 0.067 mmol) is dissolved in DCM (10 ml) and TFA (5 ml) is added. The solution is stirred for 2 h at room temperature. After evaporation *in vacuo* the residue is taken up in toluene (10 ml) and the solvent is again removed *in vacuo*. The residue is now dissolved in DCM (10 ml) and *N,N*-diisopropylethylamine (100 µl, 0.57 mmol) is

added. After stirring overnight, the mixture is evaporated *in vacuo* and the residue is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1 %TFA in water and acetonitrile. The product is dissolved in a mixture of 1 N HCl and methanol and evaporated *in vacuo* affording 25 mg of the title compound as the hydrochloride.

HPLC-MS (Method C): *m/z* = 514 (M+1); R_t = 3.3 min.

Example 45

(*S,S*)-6-(4-Amino-butyl)-3-naphthalen-2-ylmethyl-1-[4-(3-trifluoromethyl-cyclohexyloxy)-benzyl]-piperazine-2,5-dione



Step A:

Triphenylphosphine (356 mg, 1.4 mmol) and 3-trifluoromethylcyclohexanol (235 mg, 1.4 mmol) is added to a solution of the product from step B in example **44** (312 mg, 0.456 mmol) in THF (20 ml) with stirring at room temperature under nitrogen. A solution of diethyl azodicarboxylate (214 ml, 1.4 mmol) in THF (5 ml) is added dropwise during 30 min while the temperature is kept below 30 °C with cooling on an ice-bath. After stirring at room temperature for 2 days the mixture is evaporated to dryness and purified on silica with ethyl acetate/heptane (1:4) affording 400 mg of the product, which is used in the next step without further purification.

HPLC-MS (Method C): *m/z* = 836 (M+23); R_t = 6.5 min.

Step B:

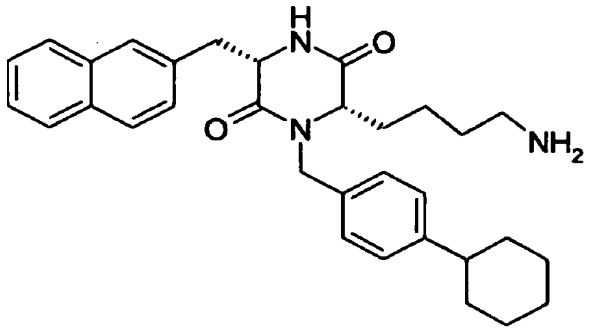
The product from step A (202 mg, 0.24 mmol) is dissolved in DCM (15 ml) and TFA (15 ml) is added. The solution is stirred for 6 h at room temperature. After evaporation *in vacuo* the residue is taken up in toluene (10 ml) and the solvent is again removed *in vacuo*. The residue is now dissolved in DCM (20 ml) and *N,N*-diisopropylethylamine (83 µl, 0.48 mmol) is added.

After stirring overnight, the mixture is evaporated *in vacuo* and the residue is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1 %TFA in water and. The product is dissolved in a mixture of 1 N HCl and methanol and evaporated *in vacuo* affording 100 mg of the title compound as the hydrochloride

HPLC-MS (Method C): *m/z* = 582 (M+1); R_t = 3.4 min.

Example 46

(*S,S*)-6-(4-Amino-butyl)-1-(4-cyclohexyl-benzyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



Step A:

To a solution of H-Lys(Boc)-OMe HCl (1.04 g, 3.5 mmol) in THF (40 ml) is added 4-cyclohexylbenzaldehyde (0.67 g, 3.5 mmol) and *N,N*-diisopropylethylamine (0.5 ml, 3 mmol), and the mixture is stirred for 4 h at room temperature. Then methanol (3.4 ml), acetic acid (1.6 ml) and sodium cyanoborohydride (0.65 g, 10 mmol) is added and the mixture is stirred overnight at room temperature. Then the mixture is evaporated *in vacuo* and the residue is taken up in ethyl acetate (150 ml) and washed with saturated aqueous sodium chloride (30 ml) and 1N sodium hydroxide (30 ml). The organic phase is dried over sodium sulfate and evaporated to dryness to give the crude product, which is used in the next step without further purification.

HPLC-MS (Method C): *m/z* = 433 (M+1); R_t = 3.7 min.

Step B:

To a solution of Boc-β-2-naphthyl-Ala-OH (1.8 g, 5.6 mmol) in THF (15 ml) is added *N,N'*-diisopropylcarbodiimide (0.35 ml, 2.8 mmol) and the mixture is stirred for 30 min at room temperature. A solution of crude product from step A (1.20 g, 2.8 mmol) in THF (15 ml) is added and the mixture is stirred for 7 h at room temperature. Then *N,N*-diisopropyl-ethylamine (0,72 ml, 5.6 mmol) is added and stirring is continued overnight. The mixture is evaporated *in vacuo* and the residue is taken up in ethyl acetate (75 ml) and washed

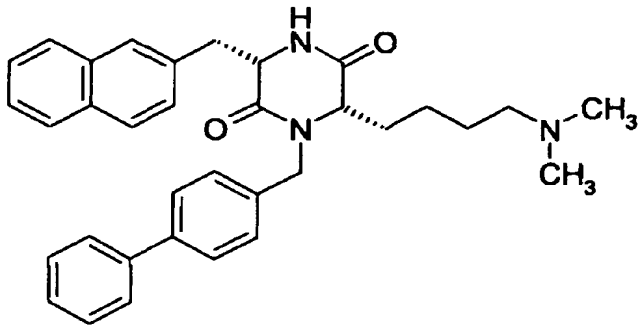
successively with 1 N HCl (50 ml) and saturated aqueous sodium hydrogen carbonate (50 ml), dried over sodium sulfate and evaporated to dryness. Column chromatography on silica with ethyl acetate/heptane (1:3 to 1:1) afforded the intermediate in a yield of 420 mg (20%). HPLC-MS (Method C): *m/z* = 752 (M+23), 730 (M+1); R_t = 6.7 min.

Step C:

The product from step B is dissolved in DCM (30 ml) followed by the addition of TFA (10 ml). The solution is stirred for 2 h at room temperature. After evaporation *in vacuo* the residue is taken up in toluene (30 ml) and the solvent is again removed *in vacuo*. The residual oil is now dissolved in DCM (20 ml) and *N,N*-diisopropylethylamine (0.98 ml, 5.6 mmol) is added. After stirring overnight, the mixture is evaporated *in vacuo* and the residue is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1 %TFA in water and acetonitrile The product is dissolved in a mixture of 1 N HCl and methanol and evaporated *in vacuo* affording 150 mg of the title compound as the hydrochloride
HPLC-MS (Method C): *m/z* = 498 (M+1); R_t = 3.4 min.

Example 47

(*S,S*)-1-Biphenyl-4-ylmethyl-6-(4-dimethylamino-butyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



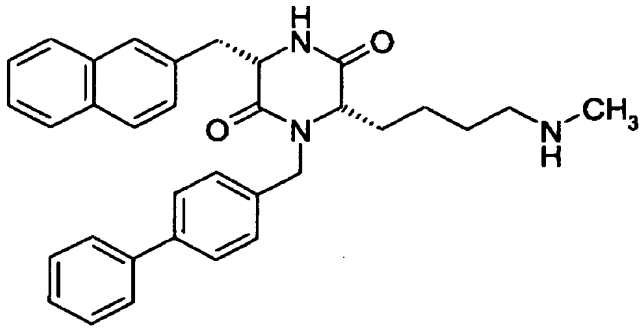
Step A:

0.123 g (0.25 mmol) of (*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-piperazine-2,5-dione (example **11**) is mixed with 1 ml of tetrahydrofuran, 0.288 ml (3.8 mmol) of 37% formalin solution, and 0.045 ml of acetic acid. The mixture is stirred for 30 minutes. 0.027 g (0.425 mmol) of sodium cyanoborohydride is added, followed by 1 ml of tetrahydrofuran and 1 ml of methanol. The mixture is stirred for 24 hours and then poured into 50 ml of 37% aqueous hydrochloric acid. After filtration, the resulting filtrate is cooled and treated with sodium hydroxide until pH = 14. The resulting precipitate is collected by

filtration, washed with water and dried *in vacuo* to give 54 mg of the product.
HPLC-MS (Method B): *m/z* = 520 (M+1); R_t = 4.43 min.

Example 48

(*S,S*)-1-Biphenyl-4-ylmethyl-6-(4-methylamino-butyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



Step A:

0.295 g (0.60 mmol) of (*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-piperazine-2,5-dione (product from example **11**) is mixed with 11 ml of dichloromethane and 0.185 ml (1.32 mmol) of triethylamine. A solution of 0.133 g (0.60 mmol) 2-nitrobenzenesulfonylchloride in 5 ml of dichloromethane is added. The mixture is stirred for 30 minutes. After addition of 25 ml of dichloromethane, the mixture is washed with 1M aqueous hydrochloric acid (4x40 ml), water (50 ml), and aqueous sodium hydrogencarbonate (40 ml). The organic phase afforded, after drying with Na_2SO_4, filtration, and evaporation, 0.385 g (0.57 mmol) of (*S,S*)-*N*-[4-(1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-yl)-butyl]-2-nitrobenzenesulfonamide.

Step B:

0.169 g (0.250 mmol) of the sulfonamide obtained by step A is mixed with 0.021 g (0.150 mmol) of potassium carbonate, 0.6 ml of dimethylformamide, and 0.036 ml (0.575 mmol) of methyl iodide. The mixture is stirred for 22 hours. The methyl iodide is evaporated off.

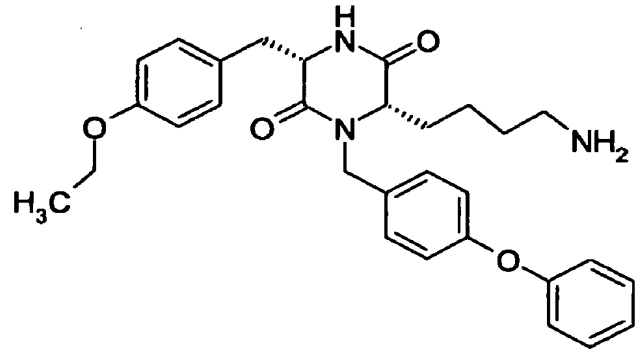
Step C:

The suspension obtained by step B is treated with 0.069 g (0.50 mmol) of potassium carbonate, 0.30 ml of dimethylformamide, and 0.070 ml (1.0 mmol) of 2-mercaptoethanol and stirred for four hours. The mixture is partitioned between 40 ml of ethyl acetate and 20 ml of 0.2 M aqueous sodium hydroxide. The organic phase is washed with 0.2 M aqueous sodium hydroxide (2x20 ml) and water (30 ml). Drying over sodium sulfate, filtration and evaporation

afforded 0.141 g of a tough yellow residue. This is dissolved in 1.5 ml of dichloromethane and eluted through a silicagel column (30 ml of "Kieselgel 60", 230-400 mesh, Macherey-Nagel GmbH & Co. KG) with ethyl acetate / methanol / aq.NH_3 (10:10:1; aq.NH_3 = 25% aqueous ammonia). The eluate is collected as 10-ml-fractions. One fraction (Rf = 0.33 with methanol / aq.NH_3 95:5 on silicagel-TLC) is evaporated to give 9 mg of the product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05-1.45 ppm (m, 6H), 2.33 ppm (m_c, 2H) overlapped with 2.36 ppm (s, 3H), 3.23 ppm (dd, J = 13.7 Hz and 8.6 Hz, 1H), 3.53 ppm (dd, J = 13.7 Hz and 3.6 Hz, 1H), 3.82 ppm (dd, J = 7.2 Hz and 3.3 Hz, 1H), 4.03 ppm (d, J = 14.8 Hz, 1H), 4.43 ppm (dd, J = 8.6 Hz and 3.6 Hz, 1H), 5.34 ppm (d, J = 14.8 Hz, 1H), 6.03 ppm (broad s, 1H), 7.30-7.57 ppm (m, 12H), 7.70 ppm (s, 1H), 7.80-7.85 ppm (m, 3H); HPLC-MS (Method B): m/z = 506 (M+1); R_t = 4.38 min.

Example 49 (General procedure (B))

(*S,S*)-6-(4-Amino-butyl)-3-(4-ethoxy-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione



Step A:

The intermediate from example **39**, Step A is used.

Step B:

5.0 mmol, 1.6 g Boc-Tyr(Et)-OH is dissolved in 15 ml THF, 0.5 equi., 390 µl DIC is added and the resulting mixture is stirred for 35 min. Then 2.5 mmol of the crude product of step A is added in 15 ml THF. After 4 h 430 µl DIPEA is added and the mixture is stirred overnight. The solvent is removed *in vacuo* and the residue is taken up in 60 ml ethyl acetate. The org. phase is washed twice with 30 ml 1 M HCl and twice with 30 ml sat. $NaHCO_3$ and dried over sodium sulfate. The solvent is removed *in vacuo* and the residual oil is purified on silica with ethyl acetate/heptane (2:3).

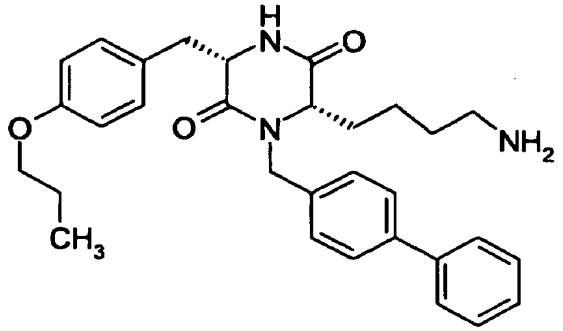
Step C:

The purified product from step B is dissolved in 30 ml DCM and 30 ml TFA is added. The solvents are removed *in vacuo* after 30 min. The residual oil is taken up in 30 ml DCM and 2.0 ml DIPEA is added. The solvent is removed *in vacuo* after 1.5 h and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

HPLC-MS (Method C): *m/z* = 502 (M+1); R_t = 2.81 min.

Example 50 (General procedure (D))

(*S,S*)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-propoxy-benzyl)-piperazine-2,5-dione



Step A:

50 mmol, 16.9 g Boc-Tyr(*t*-bu)-OH is dissolved in 150 ml THF and 0.5 equi, 3.9 ml DIC is added. The mixture is stirred for 30 min and the intermediate of example **28**, step A, 25 mmol, 10.7 g in 100 ml THF is added. After 2 h 1 equi., 4.2 ml DIPEA is added and the mixture is stirred overnight. The solvent is removed *in vacuo* and the oil is taken up in 250 ml ethyl acetate. The org. phase is washed twice with 150 ml 1M HCl and twice with 150 ml sat. $NaHCO_3$, the org. phase is dried over sodium sulfate and the solvent is removed *in vacuo*. The residual oil is purified on silica with ethyl acetate:heptane 2:3.

The pure product is dissolved in 100 ml DCM and 100 ml TFA. The solvent is removed after 15 min and the oil taken up in 150 ml DCM and 5 ml DIPEA is added and the mixture stirred at room temperature. After 20 min another 5 ml DIPEA are added and again after 3 h and 5 h. The solvent is removed *in vacuo* after 6 h and used for unpurified for the next step.

Step B:

The product of step A (14 mmol) is dissolved in 100 ml DCM and 2 equi, 6.1 ml Boc-anhydrid and 1 equi., 2.45 ml DIPEA are added. The solvent is removed *in vacuo* and the product is purified on silica using ethyl acetate.

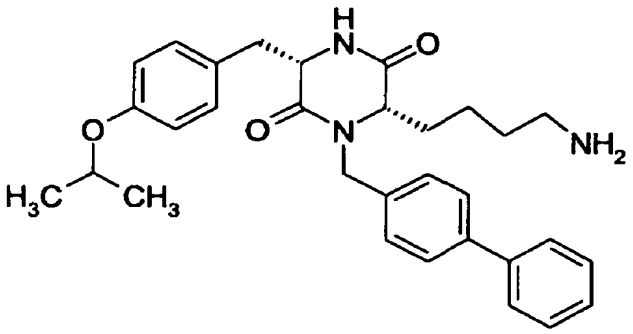
Step C:

1 mmol, 0.6 g of the product of step B is dissolved in 50 ml THF. 1 equi., 0.3 g triphenylphosphine and 1 equi., 75 µl 1-propanol are added. The reaction is started by adding 1 equi., 160 µl diethyl azadicarboxylate. The mixture is stirred over night at room temperature. The product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

Step D:

0.5 mmol, 0.3 g of the product of step C is dissolved in 25 ml DCM and 25 ml TFA. The solvent is removed *in vacuo* after 20 min and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.
HPLC-MS (Method C): *m/z* = 500 (M+1); R_t = 3.00 min.

Example 51 (General procedure (D))
(*S,S*)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-isopropoxy-benzyl)-piperazine-2,5-dione



Step A and B:

The intermediate of example **50** is used.

Step C:

0.5 mmol, 0.3 g of the product of step B is dissolved in 5 ml THF. 1.5 equi., 0.2 g triphenylphosphine and 1.5 equi., 58 µl 2-propanol are added. The reaction is started by adding 1.5 equi., 120 µl diethyl azadicarboxylate. The mixture is stirred over night at room temperature. The product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

Step D:

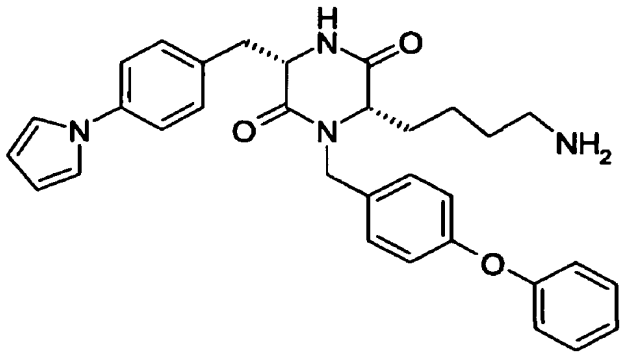
0.5 mmol, 0.3 g of the product of step C is dissolved in 25 ml DCM and 25 ml TFA. The solvent is removed *in vacuo* after 20 min and the product is purified on a C18 reverse phase

column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

HPLC-MS (Method C): *m/z* = 500 (M+1); R_t = 2.91 min.

Example 52 (General procedure (B))

(*S,S*)-6-(4-Amino-butyl)-1-(4-phenoxy-benzyl)-3-(4-pyrrol-1-yl-benzyl)-piperazine-2,5-dione



Step A:

The intermediate from example **39**, Step A is used.

Step B:

5.0 mmol, 1.7 g Boc-4-(1-pyrrolyl)-Phe-OH is dissolved in 15 ml THF, 0.5 equi., 390 µl DIC is added and the resulting mixture is stirred for 40 min. Then 2.5 mmol of the crude product of step A is added in 15 ml THF. After 4 h 430 µl DIPEA is added and the mixture is stirred overnight. The solvent is removed *in vacuo* and the residue is taken up in 50 ml ethyl acetate. The org. phase is washed twice with 30 ml 1 M HCl and twice with 30 ml sat. $NaHCO_3$ and dried over sodium sulfate. The solvent is removed *in vacuo* and the residual oil is purified on silica with ethyl acetate/heptane (2:3).

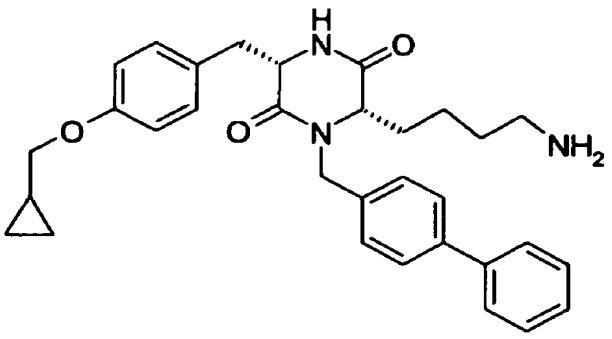
Step C:

The purified product from step B is dissolved in 25 ml DCM and 25 ml TFA is added. The solvents are removed *in vacuo* after 15 min. The residual oil is taken up in 40 ml DCM and 2.0 ml DIPEA is added. The solvent is removed *in vacuo* after 40 min and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

HPLC-MS (Method C): *m/z* = 523 (M+1); R_t = 3.15 min.

Example 53 (General procedure (D))

(*S,S*)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-cyclopropylmethoxy-benzyl)-piperazine-2,5-dione



Step A and B:

The intermediate of example **50** is used.

Step C:

0.5 mmol, 0.3 g of the product of step B is dissolved in 4 ml THF. 1.5 equi., 0.2 g triphenylphosphine in 1 ml THF and 1.5 equi., 61 µl cyclopropyl methanol are added. The reaction is started by adding 1.5 equi., 120 µl diethyl azadicarboxylate. The mixture is stirred over night at room temperature. The product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

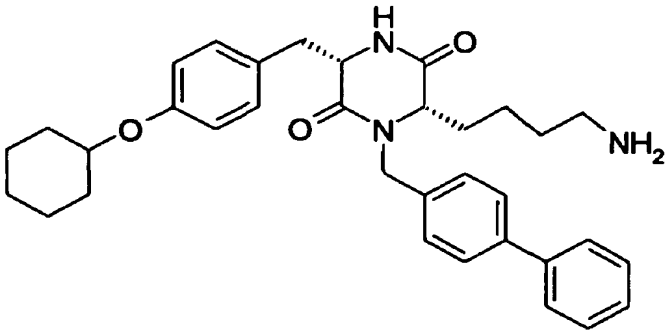
Step D:

0.4 mmol, 0.2 g of the product of step C is dissolved in 20 ml DCM and 20 ml TFA. The solvent is removed *in vacuo* after 15 min and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

HPLC-MS (Method C): *m/z* = 512 (M+1); R_t = 3.22 min.

Example 54 (General procedure (D))

(*S,S*)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-cyclohexyloxy-benzyl)-piperazine-2,5-dione



Step A and B:

The intermediate of example **50** is used.

Step C:

0.5 mmol, 0.3 g of the product of step B is dissolved in 5 ml THF. 1.5 equi., 0.2 g triphenylphosphine in 1 ml THF and 1.5 equi., 85 mg cyclohexanol in 1 ml THF are added. The reaction is started by adding 1.5 equi., 120 µl diethyl azadicarboxylate. The mixture is stirred over night at room temperature. The product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

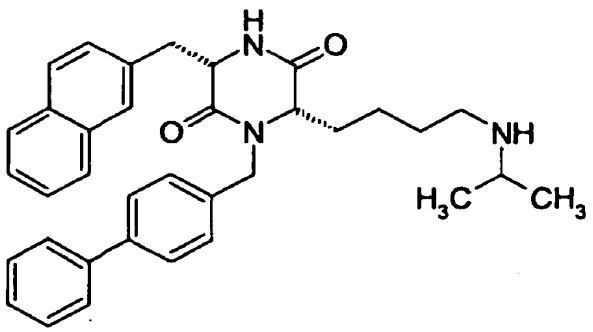
Step D:

0.2 mmol, 0.1 g of the product of step C is dissolved in 10 ml DCM and 10 ml TFA. The solvent is removed *in vacuo* after 30 min and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

HPLC-MS (Method C): *m/z* = 540 (M+1); R_t = 3.56 min.

Example 55

(*S,S*)-1-Biphenyl-4-ylmethyl-6-(4-isopropylamino-butyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



Step A:

0.143 g (0.29 mmol) of (*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-piperazine-2,5-dione (product from example **11**) is mixed with 1.5 ml of dichloromethane, 0.107 ml (1.45 mmol) of acetone, 0.045 ml of acetic acid, and 0.1 g of sodium sulfate. The mixture is stirred for 5 hours. Dichloromethane and acetone are evaporated off *in vacuo*.

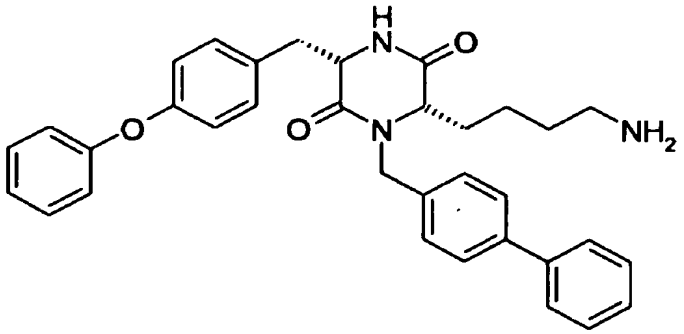
Step B:

To the residue obtained from step A, a solution of 0.031 g (0.493 mmol) of sodium cyanoborohydride in 1.5 ml of tetrahydrofuran and 0.4 ml of methanol is added, followed by 1.0 ml of dichloromethane. The mixture is stirred for two hours. The liquids are evaporated. The residue is treated with 1 ml of tetrahydrofuran and 13 ml of aqueous 37% hydrochloric acid. The resulting suspension is filtered and the filtrate is treated with solid and aqueous sodium hydroxide until pH = 14. Filtration and washing with water afforded 0.065 g of the crude product. This is dissolved in 2 ml of methanol, and 1 ml of water is added dropwise. After ice-cooling, the resulting precipitate is collected by filtration and washed with methanol / water (1:1) to give 15 mg of the product.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 ppm (s, 6H), 1.22-1.81 ppm (m, 6H), 2.40 ppm (m_c, 2H), 2.74 ppm (m_c, 1H), 3.21 ppm (dd, J = 14 Hz and 9 Hz, 1H), 3.56 ppm (d, J = 14 Hz, 1H), 3.85 ppm (m_c, 1H), 4.05 ppm (d, J = 15 Hz, 1H), 4.43 ppm (m_c, 1H), 5.35 ppm (d, J = 15 Hz, 1H), 5.90 (s, 1H), 7.30-7.58 ppm (m, 12 H), 7.70 (s, 1H), 7.78-7.85 ppm (m, 3H); HPLC-MS (Method B): m/z = 534 (M+1); R_t = 5.10 min.

Example 56

(*S,S*)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-phenoxy-benzyl)-piperazine-2,5-dione



Step A:

The intermediate of example 50, step B is used.

Step B:

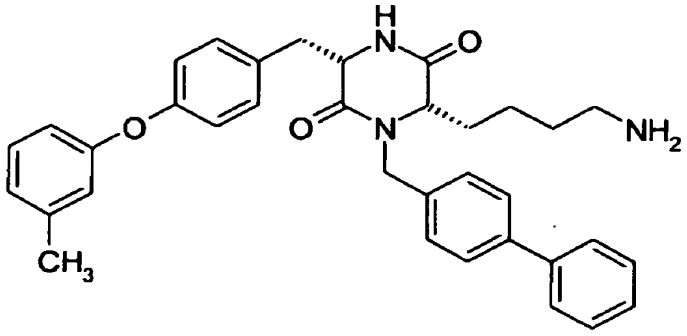
A mixture of the product of step A, $Cu(OAc)_2$ (1 equi), phenylboronic acid (2 equi), pyridine (5 equi) and crushed molecular sieves (4 Å) in dichloromethane are stirred under an air atmosphere for 72 h, filtered through a plug of silica and purified by flash chromatography (eluant ethyl acetate/heptane). Addition of 20 ml dichloromethane and 3 ml trifluoroacetic acid per 500 mg compound removed the Boc protecting group and after purification by reverse phase HPLC (water, actetonitrile, trifluoroactetic acid eluant) afforded the title compound.

^{1}H NMR ($CDCl_3$): δ 0.8-1.7 (6H, m), 2.7-3.2 (4H, m), 3.65 (1H, d), 4.05 (1H, d), 4.80 (1H, s), 5.05 (1H, d), 6.8-7.5 (18H, m), 7.8-8.1 (2H, bs).

LCMS: 534 (M+); HPLC-MS (Method C): *m/z* = 534 (M+1); R_t = 3.22 min.

Example 57

(*S,S*)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-m-tolyloxy-benzyl)-piperazine-2,5-dione



Step A:

The intermediate from example **56**, Step A, is used

Step B:

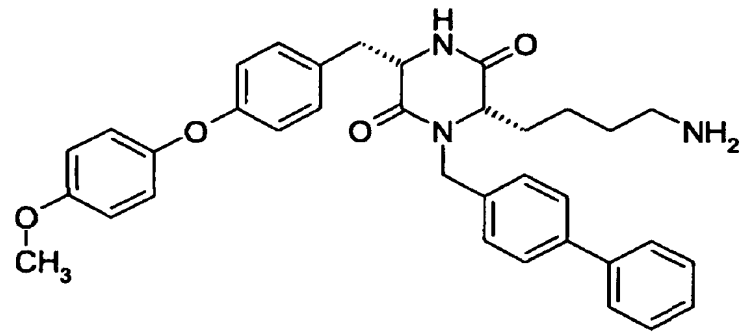
A mixture of the product of step A, $Cu(OAc)_2$ (1 equi), 3-methylphenylboronic acid (2 equi), pyridine (5 equi) and crushed molecular sieves (4 Å) in dichloromethane are stirred under an air atmosphere for 72 h, filtered through a plug of silica and purified by flash chromatography (eluant ethyl acetate/heptane). Addition of 20 ml dichloromethane and 3 ml trifluoroacetic acid per 500 mg compound removed the Boc protecting group and after purification by reverse phase HPLC (water, actetonitrile, trifluoroactetic acid eluant) afforded the title compound.

^{1}H NMR ($CDCl_3$): δ 0.9-1.7 (6H, m), 2.30 (3H, s), 2.7-3.2 (4H, m), 3.6-3.7 (1H, m), 4.05 (1H, d), 42-4.3 (1H, m), 5.10 (1H, d), 6.6-7.5 (17H, m), 7.8-8.1 (2H, bs).

LCMS: 548 (M+); HPLC-MS (Method C): *m/z* = 548 (M+1); R_t = 3.40 min.

Example 58

(*S,S*)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(4-methoxy-phenoxy)-benzyl]-piperazine-2,5-dione



Step A:

The intermediate from example **56**, Step A, is used

Step B:

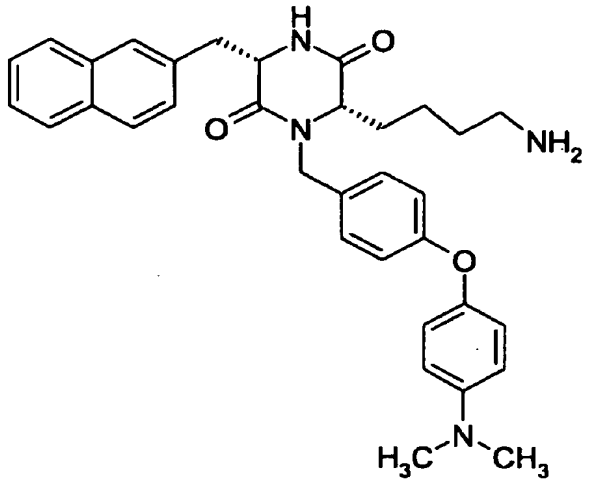
A mixture of the product of step A, $Cu(OAc)_2$ (1 equi), 4-methoxyphenylboronic acid (2 equi), pyridine (5 equi) and crushed molecular sieves (4 Å) in dichloromethane are stirred under an air atmosphere for 72 h, filtered through a plug of silica and purified by flash chromatography (eluant ethyl acetate/heptane). Addition of 20 ml dichloromethane and 3 ml trifluoroacetic acid per 500 mg compound removed the Boc protecting group and after purification by reverse phase HPLC (water, actetonitrile, trifluoroactetic acid eluant) afforded the title

compound.

HPLC-MS (Method C): *m/z* = 564 (M+1); R_t = 3.44 min.

Example 59

(*S,S*)-6-(4-Amino-butyl)-1-[4-(4-dimethylamino-phenoxy)-benzyl]-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



Step A:

A slurry of the compound obtained in example **44** step B (140 mg, 0.21 mmol), 4-(dimethylamino)phenylboronic acid (104 mg, 0.63 mmol), copper(II) acetate (76 mg, 0.42 mmol), triethylamine (146 µl, 1.05 mmol) and powdered molecular sieves (4 Å) in THF is stirred at room temperature for about two days. The mixture is filtered and the filtrate is evaporated *in vacuo*. The product is isolated from the residue by column chromatography on silica with ethyl acetate/heptane (1:2) and used directly in the following step

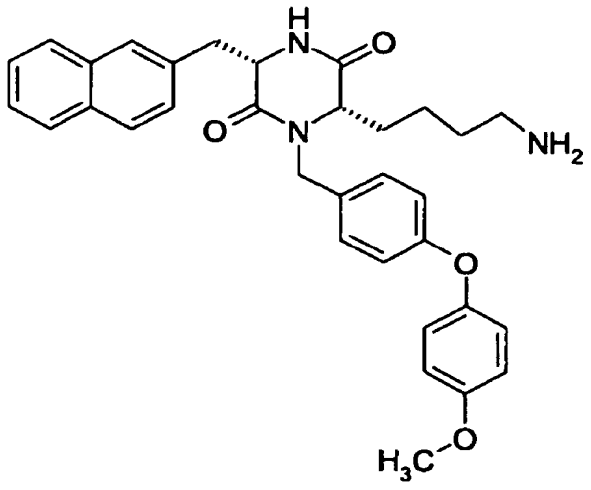
Step B:

A solution of the product from step A and TFA (3 ml) in DCM (10 ml) is stirred at room temperature overnight. After evaporation *in vacuo* the residue is taken up in toluene and the solvent is again removed *in vacuo*. The residual oil is now dissolved in DCM, and *N,N*-diisopropylethylamine (0.5 ml, 2.8 mmol) is added. After stirring overnight, the mixture is evaporated *in vacuo* and the residue is purified on preparative LC-MS. The product is dissolved in a mixture of 1 N HCl and methanol and evaporated *in vacuo* affording 30 mg of the title compound as the hydrochloride.

HPLC-MS (Method C): *m/z* = 551 (M+1); R_t = 2.2 min.

Example 60

(*S,S*)-6-(4-Amino-butyl)-1-[4-(4-methoxy-phenoxy)-benzyl]-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



Step A:

A slurry of the compound obtained in example **44** step B (140 mg, 0.21 mmol), 4-methoxyphenylboronic acid (96 mg, 0.63 mmol), copper(II) acetate (76 mg, 0.42 mmol), triethylamine (146 µl, 1.05 mmol) and powdered molecular sieves (4 Å) in THF is stirred at room temperature for about two days. The mixture is filtered and the filtrate is evaporated *in vacuo*. The product is isolated from the residue by column chromatography on silica with ethyl acetate/heptane (1:2) and used directly in the following step

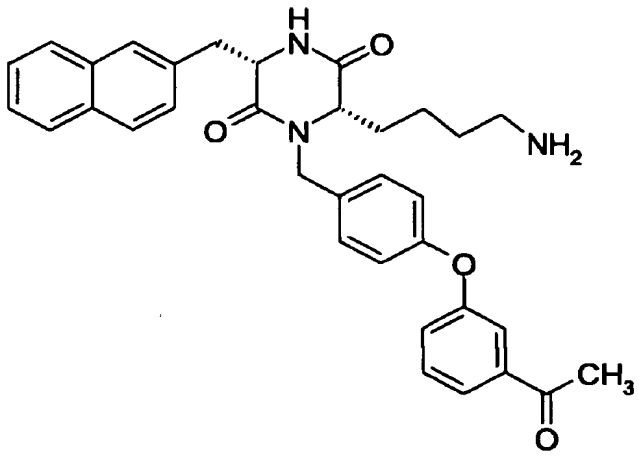
Step B:

A solution of the product from step A and TFA (3 ml) in DCM (10 ml) is stirred at room temperature overnight. After evaporation *in vacuo* the residue is taken up in toluene and the solvent is again removed *in vacuo*. The residual oil is now dissolved in DCM, and *N,N*-diisopropylethylamine (0.5 ml, 2.8 mmol) is added. After stirring overnight, the mixture is evaporated *in vacuo* and the residue is purified on preparative LC-MS. The product is dissolved in a mixture of 1 N HCl and methanol and evaporated *in vacuo* affording 85 mg of the title compound as the hydrochloride.

HPLC-MS (Method): *m/z* = 538 (M+1); R_t = 3.2 min.

Example 61

(*S,S*)-1-[4-(3-Acetyl-phenoxy)-benzyl]-6-(4-amino-butyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



Step A:

A slurry of the compound obtained in example **44** step B (140 mg, 0.21 mmol), 3-acetylphenylboronic acid (103 mg, 0.63 mmol), copper(II) acetate (76 mg, 0.42 mmol), triethylamine (146 µl, 1.05 mmol) and powdered molecular sieves (4 Å) in THF is stirred at room temperature for about two days. The mixture is filtered and the filtrate is evaporated *in vacuo*. The product is isolated from the residue by column chromatography on silica with ethyl acetate/heptane (1:2) and used directly in the following step

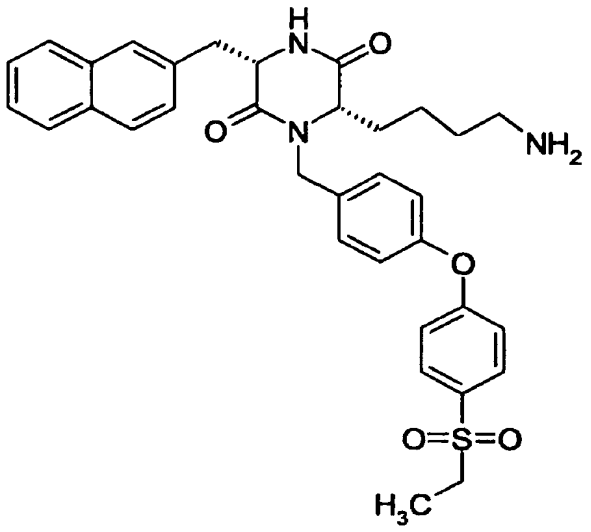
Step B:

A solution of the product from step A and TFA (3 ml) in DCM (10 ml) is stirred at room temperature overnight. After evaporation *in vacuo* the residue is taken up in toluene and the solvent is again removed *in vacuo*. The residual oil is now dissolved in DCM, and *N,N*-diisopropylethylamine (0.5 ml, 2.8 mmol) is added. After stirring overnight, the mixture is evaporated *in vacuo* and the residue is purified on preparative LC-MS. The product is dissolved in a mixture of 1 N HCl and methanol and evaporated *in vacuo* affording 85 mg of the title compound as the hydrochloride.

HPLC-MS (Method): *m/z* = 550 (M+1); R_t = 2.8 min.

Example 62

(*S,S*)-6-(4-Amino-butyl)-1-[4-(4-ethanesulfonyl-phenoxy)-benzyl]-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



Step A:

A slurry of the compound obtained in example **44** step B (140 mg, 0.21 mmol), 4-(ethylsulfonyl)phenylboronic acid (135 mg, 0.63 mmol), copper(II) acetate (76 mg, 0.42 mmol), triethylamine (146 µl, 1.05 mmol) and powdered molecular sieves (4 Å) in THF is stirred at room temperature for about two days. The mixture is filtered and the filtrate is evaporated *in vacuo*. The product is isolated from the residue by column chromatography on silica with ethyl acetate/heptane (1:2) and used directly in the following step

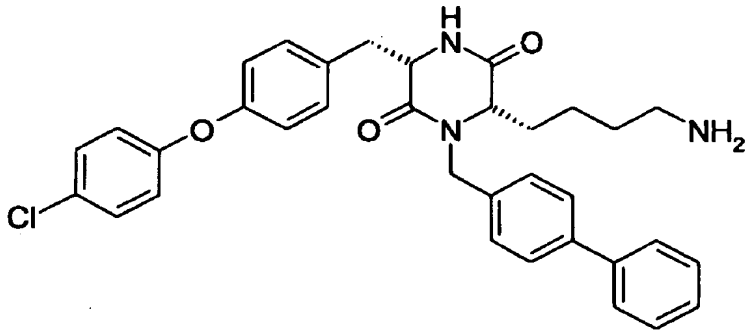
Step B:

A solution of the product from step A and TFA (3 ml) in DCM (10 ml) is stirred at room temperature overnight. After evaporation *in vacuo* the residue is taken up in toluene and the solvent is again removed *in vacuo*. The residual oil is now dissolved in DCM, and *N,N*-diisopropylethylamine (0.5 ml, 2.8 mmol) is added. After stirring overnight, the mixture is evaporated *in vacuo* and the residue is purified on preparative LC-MS. The product is dissolved in a mixture of 1 N HCl and methanol and evaporated *in vacuo* affording 50 mg of the title compound as the hydrochloride.

HPLC-MS (Method C): *m/z* = 600 (M+1); R_t = 2.9 min.

Example 63

(*S,S*)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(4-chloro-phenoxy)-benzyl]-piperazine-2,5-dione



Step A:

The intermediate from example **56**, Step A, is used

Step B:

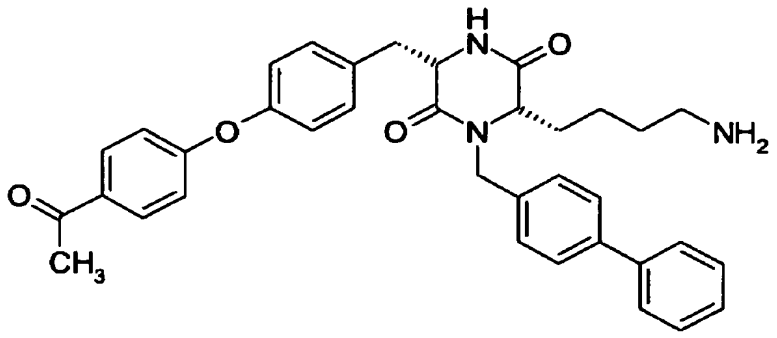
A mixture of the product of step A, $Cu(OAc)_2$ (1 equi), 4-chlorophenylboronic acid (2 equi), pyridine (5 equi) and crushed molecular sieves (4 Å) in dichloromethane are stirred under an air atmosphere for 72 h, filtered through a plug of silica and purified by flash chromatography (eluant ethyl acetate/heptane). Addition of 20 ml dichloromethane and 3 ml trifluoroacetic acid per 500 mg compound removed the Boc protecting group and after purification by reverse phase HPLC (water, actetonitrile, trifluoroactetic acid eluant) afforded the title compound.

^{1}H NMR ($CDCl_3$): δ 0.9-1.7 (6H, m), 2.7-3.2 (4H, m), 3.6-3.7 (1H, m), 4.05 (1H, d), 4.3-4.4 (1H, m), 5.10 (1H, d), 6.7-7.5 (17H, m), 7.7-7.9 (2H, bs).

LCMS: 568 (M+); HPLC-MS (Method C): *m/z* = 568 (M+1); R_t = 3.72 min.

Example 64

(*S,S*)-3-[4-(4-Acetyl-phenoxy)-benzyl]-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-piperazine-2,5-dione



Step A:

The intermediate from example **56**, Step A, is used

Step B:

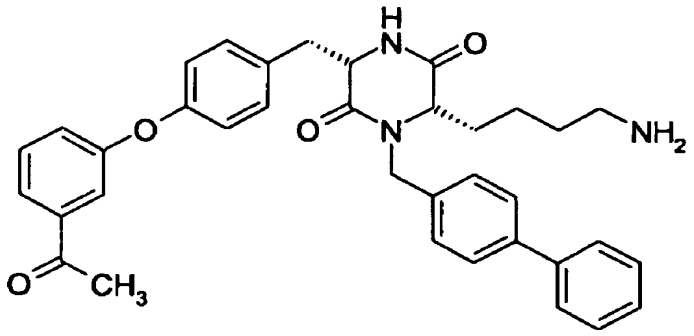
A mixture of the product of step A, $Cu(OAc)_2$ (1 equi), 4-acetylphenylboronic acid (2 equi), pyridine (5 equi) and crushed molecular sieves (4 Å) in dichloromethane are stirred under an air atmosphere for 72 h, filtered through a plug of silica and purified by flash chromatography (eluant ethyl acetate/heptane). Addition of 20 ml dichloromethane and 3 ml trifluoroacetic acid per 500 mg compound removed the Boc protecting group and after purification by reverse phase HPLC (water, actetonitrile, trifluoroactetic acid eluant) afforded the title compound.

^{1}H NMR ($CDCl_3$): δ 0.9-1.7 (6H, m), 2.50 (3H, s), 2.7-3.2 (4H, m), 3.6-3.7 (1H, m), 4.05 (1H, d), 4.3-4.4 (1H, m), 5.05 (1H, d), 6.8-7.9 (17H, m), 7.9-8.1 (2H, bs).

LCMS: 576 (M+); HPLC-MS (Method C): *m/z* = 568 (M+1); R_t = 3.72 min.

Example 65

(*S,S*)-3-[4-(3-Acetyl-phenoxy)-benzyl]-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-piperazine-2,5-dione



Step A:

The intermediate from example **50**, Step B, is used

Step B:

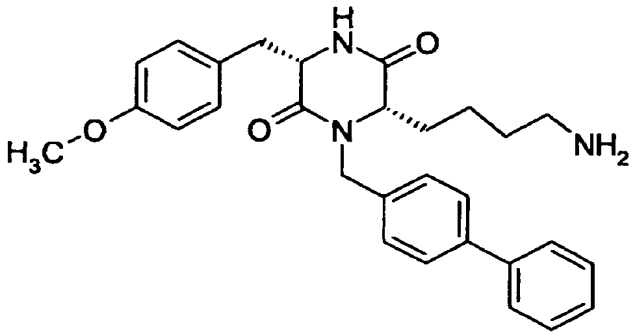
A mixture of the product of step A, $Cu(OAc)_2$ (1 equi), 3-acetylphenylboronic acid (2 equi), pyridine (5 equi) and crushed molecular sieves (4 Å) in dichloromethane are stirred under an air atmosphere for 72 h, filtered through a plug of silica and purified by flash chromatography (eluant ethyl acetate/heptane). Addition of 20 ml dichloromethane and 3 ml trifluoroacetic acid per 500 mg compound removed the Boc protecting group and after purification by reverse phase HPLC (water, actetonitrile, trifluoroactetic acid eluant) afforded the title compound.

^{1}H NMR ($CDCl_3$): δ 0.9-1.7 (6H, m), 2.50 (3H, s), 2.7-3.3 (4H, m), 3.6-3.7 (1H, m), 4.0 (1H, d), 4.3 (1H, bs), 5.05 (1H, d), 6.8-7.6 (17H, m), 7.8-8.0 (2H, bs).

LCMS: 576 (M+); HPLC-MS (Method C): *m/z* = 576 (M+1); R_t = 3.31 min.

Example 66 (General procedure (D))

(*S,S*)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-methoxy-benzyl)-piperazine-2,5-dione



Step A and B:

The intermediate of example **50** is used.

Step C:

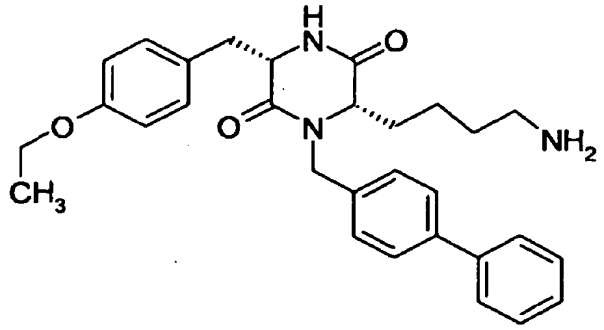
0.5 mmol, 0.3 g of the product of step B is dissolved in 5 ml THF. 1.5 equi., 0.2 g triphenylphosphine and 1.5 equi., 31 µl methanol are added. The reaction is started by adding 1.5 equi., 120 µl diethyl azadicarboxylate. The mixture is stirred over night at room temperature. The product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

Step D:

0.4 mmol, 0.2 g of the product of step C is dissolved in 10 ml DCM and 10 ml TFA. The solvent is removed *in vacuo* after 15 min and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.
HPLC-MS (Method C): *m/z* = 472 (M+1); R_t = 2.61 min.

Example 67 (General procedure (D))

(*S,S*)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-ethoxy-benzyl)-piperazine-2,5-dione



Step A and B:

The intermediate of example **50** is used.

Step C:

0.5 mmol, 0.3 g of the product of step B is dissolved in 5 ml THF. 1.5 equi., 0.2 g triphenylphosphine in 1 ml THF and 1.5 equi., 44 µl ethanol are added. The reaction is started by adding 1.5 equi., 120 µl diethyl azadicarboxylate. The mixture is stirred over night at room temperature. The product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

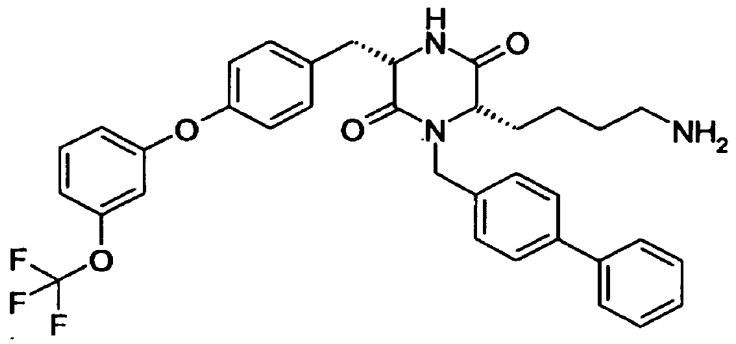
Step D:

0.4 mmol, 0.2 g of the product of step C is dissolved in 10 ml DCM and 10 ml TFA. The solvent is removed *in vacuo* after 20 min and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

HPLC-MS (Method C): *m/z* = 486 (M+1); R_t = 2.75 min.

Example 68

(*S,S*)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(3-trifluoromethoxy-phenoxy)-benzyl]-piperazine-2,5-dione



Step A:

The intermediate from example **50**, Step B, is used

Step B:

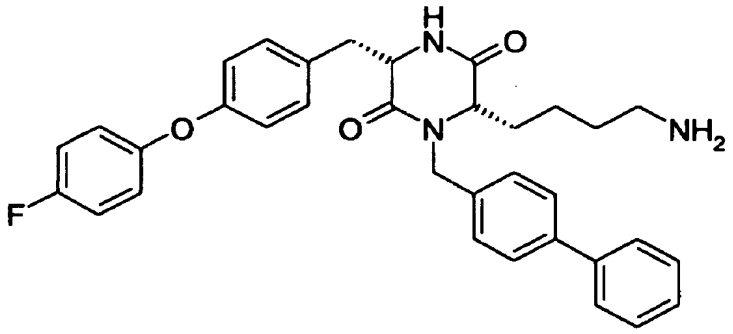
A mixture of the product of step A, $Cu(OAc)_2$ (1 equi), 3-(trifluoromethoxy) benzeneboronic acid (2 equi), pyridine (5 equi) and crushed molecular sieves (4 Å) in dichloromethane are stirred under an air atmosphere for 72 h, filtered through a plug of silica and purified by flash chromatography (eluant ethyl acetate/heptane). Addition of 20 ml dichloromethane and 3 ml trifluoroacetic acid per 500 mg compound removed the Boc protecting group and after purification by reverse phase HPLC (water, actetonitrile, trifluoroactetic acid eluant) afforded the title compound.

^{1}H NMR ($CDCl_3$): δ 0.9-1.7 (6H, m), 2.8-3.2 (4H, m), 3.6-3.7 (1H, m), 4.0 (1H, d), 4.3-4.4 (1H, m), 5.05 (1H, d), 6.7-7.5 (17H, m), 7.8-8.0 (2H, bs).

LCMS: 618 (M+); HPLC-MS (Method C): *m/z* = 618 (M+1); R_t = 3.93 min.

Example 69

(*S,S*)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(4-fluoro-phenoxy)-benzyl]-piperazine-2,5-dione



Step A:

The intermediate from example **50**, Step B, is used

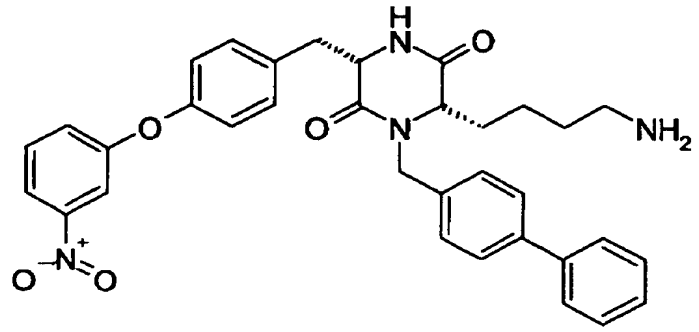
Step B:

A mixture of the product of step A, $Cu(OAc)_2$ (1 equi), 4-fluorophenylboronic acid (2 equi), pyridine (5 equi) and crushed molecular sieves (4 Å) in dichloromethane are stirred under an air atmosphere for 72 h, filtered through a plug of silica and purified by flash chromatography (eluant ethyl acetate/heptane). Addition of 20 ml dichloromethane and 3 ml trifluoroacetic acid per 500 mg compound removed the Boc protecting group and after purification by reverse phase HPLC (water, actetonitrile, trifluoroactetic acid eluant) afforded the title compound.

^{1}H NMR ($CDCl_3$): δ 0.7-1.7 (6H, m), 2.7-3.2 (4H, m), 3.6-3.7 (1H, m), 4.0 (1H, d), 4.2-4.3 (1H, m), 5.05 (1H, d), 6.7-7.5 (17H, m), 7.8-8.0 (2H, bs).

Example 70

(S,S)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(3-nitro-phenoxy)-benzyl]-piperazine-2,5-dione



Step A:

The intermediate from example **50**, Step B, is used

Step B:

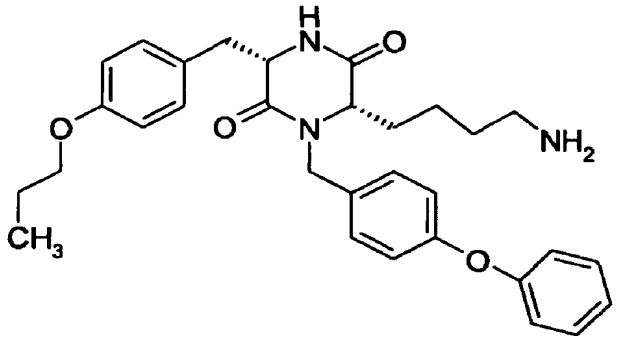
A mixture of the product of step A, $Cu(OAc)_2$ (1 equi), 3-nitrophenylboronic acid (2 equi), pyridine (5 equi) and crushed molecular sieves (4 Å) in dichloromethane are stirred under an air atmosphere for 72 h, filtered through a plug of silica and purified by flash chromatography (eluant ethyl acetate/heptane). Addition of 20 ml dichloromethane and 3 ml trifluoroacetic acid per 500 mg compound removed the Boc protecting group and after purification by reverse phase HPLC (water, actetonitrile, trifluoroactetic acid eluant) afforded the title compound.

^{1}H NMR ($CDCl_3$): δ 0.7-1.7 (6H, m), 2.7-3.3 (4H, m), 3.6-3.7 (1H, d), 4.0 (1H, d), 4.3-4.4 (1H, m), 5.1 (1H, d), 6.9-7.9 (17H, m), 7.9-8.1 (2H, bs).

LCMS: 579 (M+); HPLC-MS (Method C): *m/z* = 579 (M+1); R_t = 3.45 min.

Example 71 (General procedure (D))

(*S,S*)-6-(4-Amino-butyl)-1-(4-phenoxy-benzyl)-3-(4-propoxy-benzyl)-piperazine-2,5-dione



Step A:

45 mmol, 15.5 g Boc-Tyr(*t*-bu)-OH is dissolved in 100 ml THF and 0.5 equi, 3.5 ml DIC is added. The mixture is stirred for 30 min and the intermediate of example **39**, step A, 22 mmol, 9.9 g in 40 ml THF is added. After 2.5 h1 equi., 2.8 ml DIPEA is added and the mixture is stirred overnight. The solvent is removed *in vacuo* and the oil is taken up in 200 ml ethyl acetate. The org. phase is washed twice with 130 ml 1M HCl and twice with 130 ml sat. $NaHCO_3$, the org. phase is dried over sodium sulfate and the solvent is removed *in vacuo*. The residual oil is purified on silica with ethyl acetate:heptane 2:3.

The pure product is dissolved in 100 ml DCM and 100 ml TFA. The solvent is removed after 20 min and the oil taken up in 100 ml DCM and 5 ml DIPEA is added and the mixture stirred at room temperature. After 45 min another 5 ml DIPEA are added and again

after 2 h. The solvent is removed *in vacuo* after 3 h and the crude product used in the next step.

Step B:

The product of step A (13 mmol) is dissolved in 100 ml DCM and 2 equi, 5.5 ml Boc-anhydrid and 1 equi., 2.2 ml DIPEA are added. The solvent is removed *in vacuo* after 2 hand the product is purified on silica using ethyl acetate.

Step C:

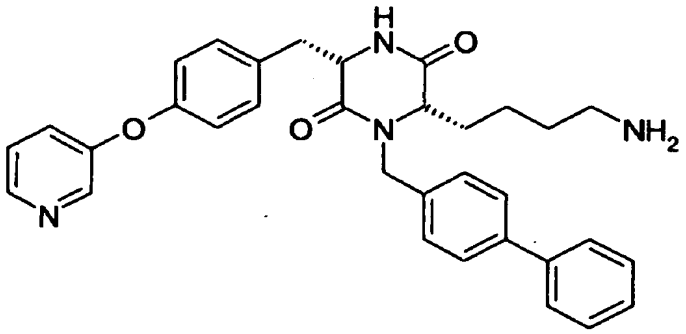
1 mmol, 0.6 g of the product of step B is dissolved in 50 ml THF. 1 equi., 0.3 g triphenylphosphine and 1 equi., 75 µl 1-propanol are added. The reaction is started by adding 1 equi., 160 µl diethyl azadicarboxylate. The mixture is stirred over night at room temperature. The product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

Step D:

0.5 mmol, 0.3 g of the product of step C is dissolved in 25 ml DCM and 25 ml TFA. The solvent is removed *in vacuo* after 20 min and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.
HPLC-MS (Method C): *m/z* = 516 (M+1); R_t = 2.90 min.

Example 72

(*S,S*)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(pyridin-3-yloxy)-benzyl]-piperazine-2,5-dione



Step A:

The intermediate from example **50**, Step B, is used

Step B:

A mixture of the product of step A, $Cu(OAc)_2$ (1 equi), pyridine-3-boronic acid (2 equi), pyridine (5 equi) and crushed molecular sieves (4 Å) in dichloromethane are stirred

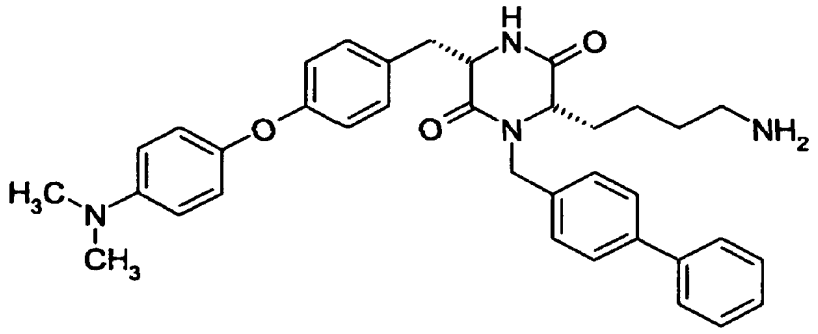
under an air atmosphere for 72 h, filtered through a plug of silica and purified by flash chromatography (eluant ethyl acetate/heptane). Addition of 20 ml dichloromethane and 3 ml trifluoroacetic acid per 500 mg compound removed the Boc protecting group and after purification by reverse phase HPLC (water, actetonitrile, trifluoroactetic acid eluant) afforded the title compound.

^{1}H NMR ($CDCl_3$): δ 0.7-1.7 (6H, m), 2.7-3.3 (4H, m), 3.6-3.7 (1H, d), 3.95 (1H, d), 4.4-4.5 (1H, m), 5.2 (1H, d), 7.0-8.5 (19H, m).

LCMS: 535 (M+); HPLC-MS (Method C): *m/z* = 535 (M+1); R_t = 2.69 min.

Example 73

(*S,S*)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(4-dimethylamino-phenoxy)-benzyl]-piperazine-2,5-dione



Step A:

The intermediate from example **50**, Step B, is used

Step B:

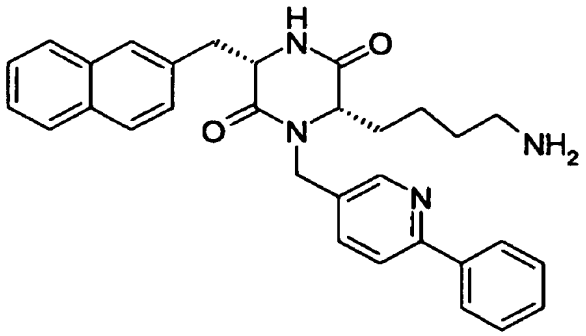
A mixture of the product of step A, $Cu(OAc)_2$ (1 equi), 4-dimethylamino phenylboronic acid (2 equi), pyridine (5 equi) and crushed molecular sieves (4 Å) in dichloromethane are stirred under an air atmosphere for 72 h, filtered through a plug of silica and purified by flash chromatography (eluant ethyl acetate/heptane). Addition of 20 ml dichloromethane and 3 ml trifluoroacetic acid per 500 mg compound removed the Boc protecting group and after purification by reverse phase HPLC (water, actetonitrile, trifluoroactetic acid eluant) afforded the title compound.

^{1}H NMR ($CDCl_3$): δ 0.7-1.7 (6H, m), 2.7-3.3 (4H, m), 3.05 (6H, s), 3.6-3.7 (1H, d), 4.0 (1H, d), 4.3-4.4 (1H, m), 5.1 (1H, d), 6.8-7.5 (17H, m), 7.8-8.0 (2H, bs).

LCMS: 577 (M+); HPLC-MS (Method C): *m/z* = 577 (M+1); R_t = 2.46 min.

Example 74

(*S,S*)-6-(4-Amino-butyl)-3-naphthalen-2-ylmethyl-1-(6-phenyl-pyridin-3-ylmethyl)-piperazine-2,5-dione



Step A:

To a solution of H-Lys(Boc)-OMe HCl (0.47 g, 1.57 mmol) in THF (15 ml) is added 6-phenyl-nicotinaldehyde (289 mg, 1.58 mmol) and *N,N*-diisopropylethylamine (0.30 ml, 1.73 mmol), and the mixture is stirred in the presence of powdered molecular sieves (4 Å) overnight at room temperature. Then methanol (1.6 ml), acetic acid (0.8 ml) and sodium cyanoborohydride (0.30 g, 4.7 mmol) is added and the mixture is stirred for 5 h at room temperature. The mixture is evaporated *in vacuo* and the residue is taken up in ethyl acetate (30 ml) and filtered. The filtrate is washed with 1N sodium hydroxide (25 ml), dried over sodium sulfate and evaporated to dryness to give 645 mg (97%) of the crude product, which is used in the next step without further purification.

HPLC-MS (Method C): *m/z* = 428 (M+1); R_t = 2.8 min.

Step B:

To a solution of Boc-β-2-naphthyl-Ala-OH (693 mg, 2.2 mmol) in THF (8 ml) is added *N,N'*-diisopropylcarbodiimide (1.1 ml, 7.1 mmol) and the mixture is stirred for 35 min at room temperature. A solution of the crude product from step A in THF (10 ml) is added and the mixture is stirred overnight at room temperature. Then *N,N*-diisopropylethylamine (0.38 ml, 2.2 mmol) is added and stirring is continued overnight. The mixture is evaporated *in vacuo* and the residue is taken up in ethyl acetate (50 ml) and washed successively with 1 N HCl (30 ml) and saturated aqueous sodium hydrogen carbonate (30 ml), dried over sodium sulfate and evaporated to dryness. Column chromatography on silica with ethyl acetate/-heptane (1:2) afforded the intermediate in a yield of 0.61 g (55%).

HPLC-MS (Method C): *m/z* = 725 (M+1); R_t = 5.4 min.

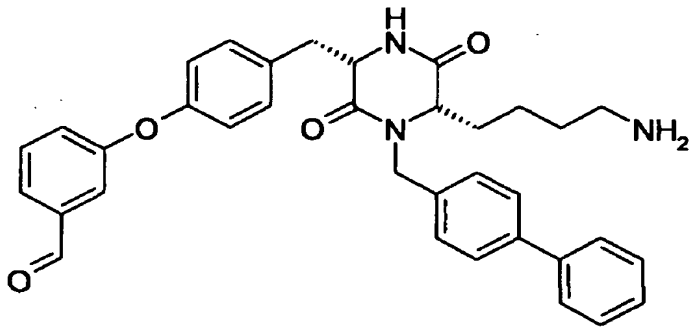
Step C:

A solution of the product from step B (534 mg, 0.74 mmol) and TFA (10 ml) in DCM (20 ml) is stirred for 2 h at room temperature. After evaporation *in vacuo* the residue is taken up in toluene (10 ml) and the solvent is again removed *in vacuo*. The residue is now dissolved in DCM (20 ml) and *N,N*-diisopropylethylamine (0.40 ml, 2.3 mmol) is added. After stirring overnight, the mixture is evaporated *in vacuo* and the residue is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1 %TFA in water and acetonitrile. The product is dissolved in a mixture of 1 N HCl and methanol and evaporated *in vacuo* affording 200 mg of the title compound as the hydrochloride

HPLC-MS (Method C): m/z = 493 (M+1); R_t = 2.5 min.

Example 75

(*S,S*)-3-{4-[5-(4-Amino-butyl)-4-biphenyl-4-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl]-phenoxy}-benzaldehyde



Step A:

The intermediate from example **50**, Step B, is used

Step B:

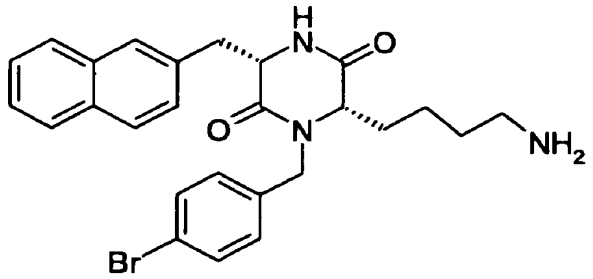
A mixture of the product of step A, $Cu(OAc)_2$ (1 equi), 3-formylphenylboronic acid (2 equi), pyridine (5 equi) and crushed molecular sieves (4 Å) in dichloromethane are stirred under an air atmosphere for 72 h, filtered through a plug of silica and purified by flash chromatography (eluant ethyl acetate/heptane). Addition of 20 ml dichloromethane and 3 ml trifluoroacetic acid per 500 mg compound removed the Boc protecting group and after purification by reverse phase HPLC (water, actetonitrile, trifluoroactetic acid eluant) afforded the title compound.

^{1}H NMR (DMSO-d_6): δ 0.7-1.7 (6H, m), 2.7-3.3 (4H, m), 3.6-3.7 (1H, d), 4.0 (1H, d), 4.35 (1H, s), 5.1 (1H, d), 6.7-7.5 (17H, m), 7.9-8.1 (2H, bs), 9.9 (1H, s).

LCMS: 562 (M+);

Example 76

(*S,S*)-6-(4-Amino-butyl)-1-(4-bromo-benzyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



Step A:

To a solution of H-Lys(Boc)-OMe HCl (5.0 g, 16.7 mmol) in THF (150 ml) is added 4-bromobenzaldehyde (3.1 g, 16.7 mmol) and *N,N*-diisopropylethylamine (3.0 ml, 16.7 mmol), and the mixture is stirred in the presence of powdered molecular sieves (4 Å) for 4 h at room temperature. Then methanol (17 ml), acetic acid (8.0 ml) and sodium cyanoborohydride (3.1 g, 50 mmol) is added and the mixture is stirred for two days at room temperature. The mixture is evaporated *in vacuo* and the residue is taken up in ethyl acetate (100 ml) and filtered. The filtrate is washed with 1N sodium hydroxide (75 ml), dried over sodium sulfate and evaporated to dryness *in vacuo* to give the crude product, which is used in the next step without further purification.

HPLC-MS (Method C): *m/z* = 429/431 (M+1); R_t = 2.8 min.

Step B:

To a solution of Boc-β-2-naphthyl-Ala-OH (8.52 g, 27 mmol) in THF (100 ml) is added *N,N'*-diisopropylcarbodiimide (2.1 ml, 13.5 mmol) and the mixture is stirred for 30 min at room temperature. A solution of the crude product from step A (5.7 g, 13.5 mmol) in THF (100 ml) is added and the mixture is stirred overnight at room temperature. Then *N,N*-diisopropyl-ethylamine (5.0 ml, 27 mmol) is added and stirring is continued overnight. The mixture is evaporated *in vacuo* and the residue is taken up in ethyl acetate (100 ml) and washed successively with 1 N HCl (50 ml) and saturated aqueous sodium hydrogen carbonate (50 ml), dried over sodium sulfate and evaporated to dryness. Column chromatography on silica with ethyl acetate/heptane (1:2) afforded the intermediate in a yield of 0.30 g (3%).

HPLC-MS (Method C): *m/z* = 748/750 (M+23); R_t = 6.1 min.

Step C:

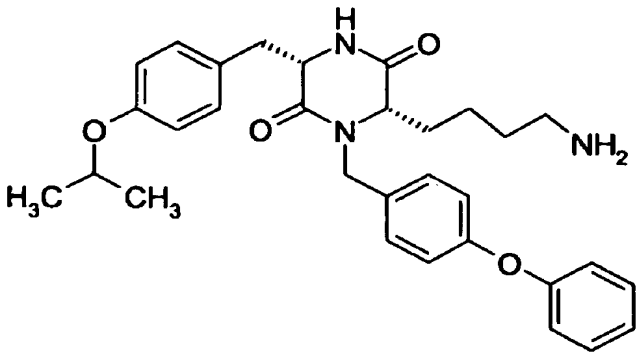
A solution of the product from step B and TFA (10 ml) in DCM (20 ml) is stirred for 2 h at room temperature. After evaporation *in vacuo* the residue is taken up in toluene (20 ml) and the solvent is again removed *in vacuo*. The residue is now dissolved in DCM (20 ml) and

N,N-diisopropylethylamine (0.8 ml, 4.6 mmol) is added. After stirring overnight, the mixture is evaporated *in vacuo* and the residue is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1 %TFA in water and acetonitrile affording. The product is dissolved in a mixture of 1 N HCl and methanol and evaporated *in vacuo* affording 123 mg (60%) of the title compound as the hydrochloride.

HPLC-MS (Method C): *m/z* = 494/496 (M+1); R_t = 2.7 min.

Example 77

(*S,S*)-6-(4-Amino-butyl)-3-(4-isopropoxy-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione



Step A and B:

The intermediate of example **71**, step B is used.

Step C:

0.5 mmol, 0.3 g of the product of step B is dissolved in 5 ml THF. 1.5 equi., 0.2 g triphenylphosphine and 1.5 equi., 58 µl 2-propanol are added. The reaction is started by adding 1.5 equi., 120 µl diethyl azadicarboxylate. The mixture is stirred for 6 h at room temperature. The product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

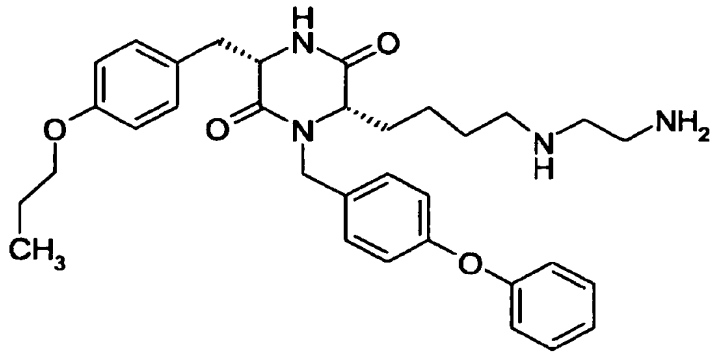
Step D:

0.3 mmol, 0.2 g of the product of step C is dissolved in 15 ml DCM and 15 ml TFA. The solvent is removed *in vacuo* after 20 min and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

HPLC-MS (Method C): *m/z* = 516 (M+1); R_t = 2.90 min.

Example 78

(*S,S*)-6-[4-(2-Amino-ethylamino)-butyl]-1-(4-phenoxy-benzyl)-3-(4-propoxy-benzyl)-piperazine-2,5-dione



Step A:

1.35 g (2.6 mmol) of example **71** is dissolved in 40 ml acetonitril. 0.6 g (1 equi.) 2-(Boc-amino)-ethylbromide, 0.2 g (0.5 equi.) potassium iodide and 1.15 ml 1,8-diazabicyclo[5.4]undec-7-ene (DBU) are added. The mixture is stirred for 4 days and then the solvent is removed *in* vacuo and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

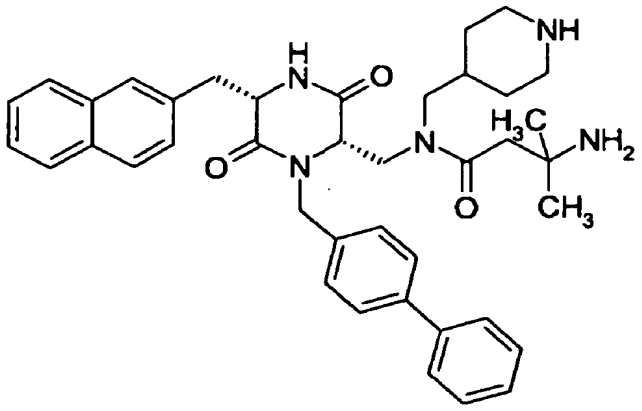
Step B:

0.7 g (1.1 mmol) of the product from step A is dissolved in 30 ml dichlormethane and 30 ml TFA. The solvent is removed *in* vacuo after 20 min and the product is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

HPLC-MS (Method C): *m/z* = 559 (M+1); R_t = 2.62 min.

Example 79

(*S,S*)-3-Amino-*N*-(1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-3-methyl-*N*-piperidin-4-ylmethyl-butyramide



Step A:

To a solution of 2-*tert*-butoxycarbonylamino-3-(9H-fluoren-9-ylmethoxy carbonylamino)-propionic acid (5.00 g, 11.72 mmol) in 100 ml of tetrahydrofuran are added 1-hydroxybenzotriazole (3.59 g, 23.44 mmol), N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride (2.36 g, 12.31 mmol) and N-ethyldiisopropylamin (2.81 ml, 16.41 mmol). Stirred for 30 min, then 20 ml of methanol is added. Stirred overnight to give a clear yellow mixture. The mixture is concentrated *in vacuo*, dissolved in 150 ml of ethyl acetate and washed with 25 ml of aqueous sodium hydrogen sulfate (10%), 25 ml of aqueous sodium hydrogen carbonate (saturated), 25 ml of water, and 25 ml of brine, dried over magnesium sulfate and filtered. Concentrated *in vacuo* to give 4.80 g (93%) of (S)-2-*tert*-butoxycarbonyl-amino-3-(9H-fluoren-9-ylmethoxycarbonylamino)propionic acid methyl ester as colorless crystalline oil.

HPLC-MS: R_t = 6.80min., (M+1) = 441, %Area by ELS = 95

Step B:

(S)-2-*tert*-Butoxycarbonylamino-3-(9H-fluoren-9-ylmethoxycarbonylamino)propionic acid methyl ester (4.80 g, 10.90 mmol) is dissolved in 20 ml of ethyl acetate in a 250 ml flask equipped with a magnetic stirrer. To the stirred solution is added 80 ml of 2.8 M hydrogen chloride in ethyl acetate and the reaction is stirred for 2 hours under nitrogen. Concentrated *in vacuo* to give a white solid, which is taken up in ethyl acetate, stirred and filtered. The solid is dried *in vacuo* at 40 °C to give 3.00 g (73%) of ((S)-2-amino-3-(9H-fluoren-9-ylmethoxycarbonylamino)propionic acid methyl ester hydrochloride as a white solid.

HPLC-MS: R_t = 4.43 min., (M+1) = 341, %Area by ELS = 94

Step C:

((S)-2-Amino-3-(9H-fluoren-9-ylmethoxycarbonylamino)propionic acid methyl ester hydrochloride (2.98 g, 7.91 mmol) is dissolved in a mixture of 40 ml of tetrahydrofuran and 40 ml of methanol. Sodium acetate (2.59 g, 31.6 mmol), biphenyl-4-carbaldehyde (1.44 g, 7.91 mmol), molecular sieves (4Å) and sodium cyanoborohydride (8.7 ml, 8.7 mmol) is added. Stirred overnight under nitrogen. Filtered through Hyflo Super Cel® to give a clear solution which is concentrated *in vacuo*, dissolved in 100 ml of ethyl acetate and washed with 25 ml of aqueous sodium hydrogen carbonate (saturated), 25 ml of water, 25 ml of brine, dried over magnesium sulfate and filtered. Addition of 5 ml 2.8 M hydrogen chloride in ethyl acetate resulted in precipitation of a white solid, which is isolated by filtration and dried to afford 4.01 g (93%) of (2S)-2-[(biphenyl-4-ylmethyl)amino]-3-(9H-fluoren-9-ylmethoxycarbonylamino)propionic acid methyl ester hydrochloride.

Step D:

To a solution of (S)-2-*tert*-butoxycarbonylamino-3-(2-naphtyl)propionic acid (4.65 g, 14.7 mmol) in 30 ml of tetrahydrofuran is added N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride (1.41 g, 7.37 mmol). Stirred for 30 min, then (2S)-2-[(biphenyl-4-ylmethyl)amino]-3-(9H-fluoren-9-ylmethoxycarbonylamino)propionic acid methyl ester hydrochloride (4.00 g, 7.37 mmol) and N-ethyldiisopropylamin (2.52 ml, 14.7 mmol) are added. Stirred for 3 days. The mixture is concentrated *in vacuo*, dissolved in 100 ml of ethyl acetate and 25 ml of aqueous sodium hydrogen sulfate (10%), mixed and separated. The aqueous phase is extracted with 50 ml of ethyl acetate and the combined organic phases are washed with 25 ml of water, 25 ml of brine, dried over magnesium sulfate and filtered. Concentrated *in vacuo* to give 7.62 g of yellow foam, which is analyzed by LC-MS, indicating only 16 % of (2S)-2-[biphenyl-4-ylmethyl-(2S)-(2-*tert*-butoxycarbonylamino-3-(2-naphthyl)propionyl)amino]-3-(9H-fluoren-9-ylmethoxycarbonylamino)propionic acid methyl ester. The crude product is dissolved in 50 ml of tetrahydrofuran and 2-*tert*-butoxycarbonylamino-3-(2-naphtyl)propionic acid (2.32 g, 7.37 mmol), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (3.44 g, 7.37 mmol) and N-ethyldiisopropylamin (1.26 ml, 7.37 mmol) are added. Stirred overnight and concentrated *in vacuo*. Taken up in 150 ml of dichloromethane and filtered through Hyflo Super Cel®. The clear filtrate is washed with 50 ml of aqueous sodium hydrogen sulfate (10%), 50 ml of aqueous sodium hydrogen carbonate (saturated), 50 ml of water, and 50 ml of brine, dried over magnesium sulfate and filtered. Purified by flash chromatography (400 g of SiO_2, (heptane:ethyl acetate (1:1)) to give 1.25 g (21%) of (2S)-2-[biphenyl-4-ylmethyl-(2S)-(2-*tert*-butoxycarbonylamino-3-(2-naphthyl)-propionyl)amino]-3-(9H-fluoren-9-ylmethoxycarbonylamino)propionic acid methyl ester.
HPLC-MS: R_t = 8.83 min., (M+1) = 804, %Area by ELS = 45

Step E:

To a solution of (2S)-2-[biphenyl-4-ylmethyl-(2S)-(2-*tert*-butoxycarbonylamino-3-(2-naphthyl)propionyl)amino]-3-(9H-fluoren-9-ylmethoxycarbonylamino)propionic acid methyl ester (1.20 g, 1.49 mmol) in 20 ml of dichloromethane is added 20 ml of trifluoroacetic acid. Stirred for 2 hours, after which the solvent is removed *in vacuo*. Stripped 2 times from dichloromethane to afford 1.26 g (theoretically 1.49 mmol) of (2S)-2-[((2S)-2-amino-3-(2-naphthyl)propionyl)biphenyl-4-ylmethylamino]-3-(9H-fluoren-9-ylmethoxy carbonylamino)propionic acid methyl ester trifluoroacetic acetate as yellow foam.
HPLC-MS: Rt = 6.93 min., (M+1) = 705, %Area by ELS = 40

Step F:

To a solution of (2S)-2-[((2S)-2-amino-3-(2-naphthyl)propionyl)biphenyl-4-ylmethylamino]-3-(9H-fluoren-9-ylmethoxycarbonylamino)propionic acid methyl ester trifluoroacetic acetate in 20 ml of dichloromethane is added 2 ml of N-ethyldiisopropylamin. Stirred for 4 hours, then 80 ml of dichloromethane is added, and the mixture is washed with 20 ml of aqueous sodium hydrogen sulfate (10%), 20 ml of aqueous sodium hydrogen carbonate (saturated), 20 ml of brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford 1.02 g (theoretically 1.49 mmol) of ((2S,5S)-1-Biphenyl-4-ylmethyl-5-(2-naphthyl)methyl-3,6-dioxo-piperazin-2-ylmethyl)carbamic acid 9H-fluoren-9-ylmethyl ester as yellow foam.
HPLC-MS: Rt = 7.90 min., (M+1) = 672, %Area by ELS = 96

Step G:

To a solution of ((2S,5S)-1-biphenyl-4-ylmethyl-5-(2-naphthyl)methyl-3,6-dioxo-piperazin-2-ylmethyl)carbamic acid 9H-fluoren-9-ylmethyl ester (theoretically 1.49 mmol) in 10 ml of dichloromethane is added 10 ml of tris(2-aminoethyl)amine. Stirred for 2 hours under nitrogen. The mixture is added 30 ml of dichloromethane and 30 ml of brine, mixed and separated. The aqueous phase is extracted 2 times with 20 of dichloromethane, and the combined organic phases are washed with 3 times of 30 ml of aqueous phosphate buffer (pH: 6.6), 20 ml of brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford 0.50 g (74%) of (3S,6S)-6-Aminomethyl-1-biphenyl-4-ylmethyl-3-(2-naphthyl)methylpiperazine-2,5-dione as yellow foam.
HPLC-MS: Rt = 4.86 min., (M+1) = 450, %Area by ELS = 100

Step H:

To a solution of (3S,6S)-6-aminomethyl-1-biphenyl-4-ylmethyl-3-(2-naphthyl)methylpiperazine-2,5-dione (0.15 g, 0.33 mmol) in 5 ml of tetrahydrofuran and 5 ml of methanol is added sodium acetate (0.11 g, 1.32 mmol), 4-formyl-piperidine-1-carboxylic acid *tert*-butyl ester (0.070 g, 0.33 mmol), molecular sieves (4Å) and 1.0 M sodium

cyanoborohydride (0.33 ml, 0.33 mmol) in tetrahydrofuran. Stirred overnight and then filtered through Hyflo Super Cel®. Concentrated *in vacuo*, dissolved in 50 ml of dichloromethane and washed with 10 ml of aqueous sodium hydrogen carbonate (saturated), 10 ml of brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford 0.21 g (100%) of 4-{[((2S,5S)-1-biphenyl-4-ylmethyl-5-(2-naphthyl)methyl-3,6-dioxo-piperazin-2-ylmethyl)amino]methyl}piperidine-1-carboxylic acid *tert*-butyl ester as orange oil.
HPLC-MS: Rt = 5.57 min., (M+1) = 647, %Area by ELS = 87

Step I:

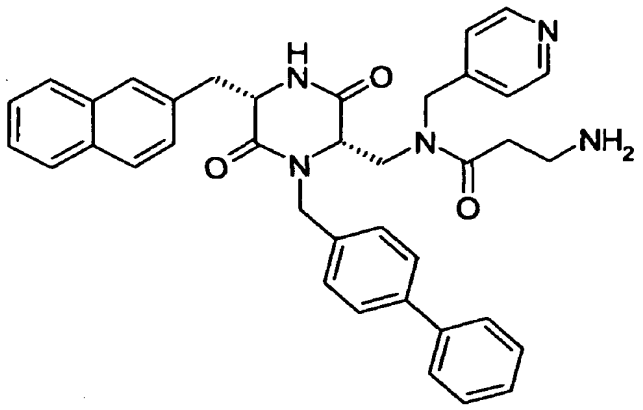
To a solution of 3-*tert*-butoxycarbonylamino-3-methyl-butyric acid (0.034 g, 0.16 mmol) in 5 ml of dichloromethane is added 1-hydroxy-7-azabenzotriazole (0.021 g, 0.16 mmol) and N-ethyl-N'-(3-dimethylaminopropyl)-carbodiimide hydrochloride (0.030 g, 0.16 mmol). Stirred for 30 min after which 4-{[((2S,5S)-1-biphenyl-4-ylmethyl-5-(2-naphthyl)methyl-3,6-dioxo-piperazin-2-ylmethyl)amino]methyl}piperidine-1-carboxylic acid *tert*-butyl ester (0.10 g, 0.16 mmol) and N-ethyldiisopropylamin (0.035 ml, 0.20 mmol) are added. Stirred overnight to give a clear yellow solution. The mixture is added to 10 ml of dichloromethane and 5 ml of aqueous sodium hydrogen sulfate (10%), mixed and separated. The aqueous phase is extracted with 5 ml of dichloromethane, and the combined organic phases are washed with 5 ml of aqueous sodium hydrogen carbonate (saturated), 5 ml of brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford 0.15 g (theoretically 0.16 mmol) of 4-{[((2S,5S)-1-biphenyl-4-ylmethyl-5-(2-naphthyl)methyl-3,6-dioxo-piperazin-2-ylmethyl)-(3-*tert*-butoxycarbonylamino-3-methyl-butyryl)amino]methyl}piperidine-1-carboxylic acid *tert*-butyl ester as yellow oil.
HPLC-MS: Rt = 8.20 min., (M+1) = 847, %Area by ELS = 89

Step J:

To a solution of 4-{[((2S,5S)-1-biphenyl-4-ylmethyl-5-(2-naphthyl)methyl-3,6-dioxo-piperazin-2-ylmethyl)-(3-*tert*-butoxycarbonylamino-3-methyl-butyryl)amino]methyl}piperidine-1-carboxylic acid *tert*-butyl ester in 5 ml of dichloromethane is added 5 ml of trifluoroacetic acid. Stirred for 2 hours, concentrated *in vacuo*, stripped 2 times from dichloromethane. Purified by preparative HPLC (20-40% acetonitrile in water /0.1% trifluoroacetic acid, 40 min). The obtained pure fractions are combined and 1 ml of 1N aqueous hydrogen chloride is added. The compound is lyophilized to give 55 mg (52%) of the title compound as a hydrochloride salt.
HPLC (A): R_t = 30.17 min., 99 % (214 nm); HPLC (B): R_t = 32.87 min., 99 % (214 nm);HPLC-MS: R_t = 4.30 min., (M+1) = 646, %Area by ELS = 100

Example 80

(*S,S*)-3-Amino-*N*-(1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-*N*-pyridin-4-ylmethyl-propionamide



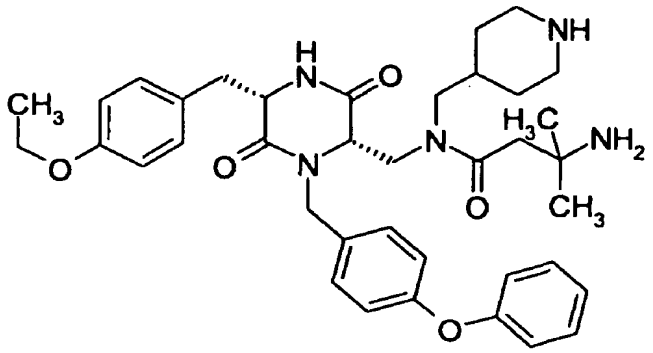
21.5 mg of the title compound is synthesized as described for (*S,S*)-3-amino-*N*-(1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-3-methyl-*N*-piperidin-4-ylmethyl-butyramide using pyridine-4-carbaldehyde instead of 4-formyl-piperidine-1-carboxylic acid *tert*-butyl ester and 3-*tert*-butoxycarbonylamino-propionic acid instead of 3-*tert*-butoxycarbonylamino-3-methyl-butyric acid.

The title compound is purified by preparative HPLC (20-40% acetonitrile in water /0.1% trifluoroacetic acid, 40 min). To the combined pure fractions are added 1 ml of 1 M aqueous hydrogen chloride and the mobile phase is removed by lyophilisation.

HPLC (A1): R_t = 28.77 min., 100 % (214 nm); HPLC (B1): R_t = 30.66 min., 100 % (214 nm);HPLC-MS: R_t = 4.23 min., (M+1) = 612, %Area by ELS = 100

Example 81

(*S,S*)-3-Amino-*N*-[5-(4-ethoxy-benzyl)-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-3-methyl-*N*-piperidin-4-ylmethyl-butyramide



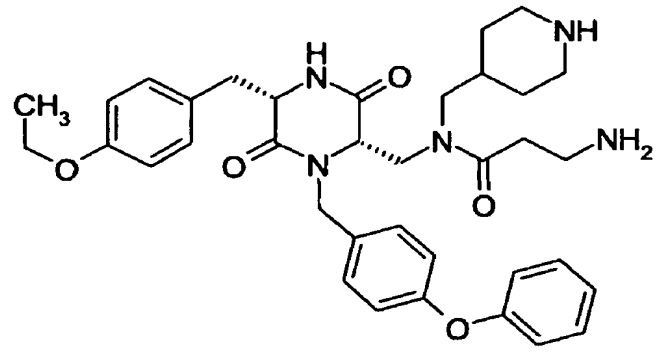
55 mg of the title compound is synthesized as described for (*S,S*)-3-amino-*N*-(1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-3-methyl-*N*-piperidin-4-ylmethyl-butyramide using 4-phenoxybenzaldehyde instead of biphenyl-4-carbaldehyde and (S)-2-*tert*-butoxycarbonylamino-3-(4-ethoxyphenyl)propionic acid instead of (S)-2-*tert*-butoxycarbonylamino-3-(2-naphtyl)propionic acid.

The title compound is purified by preparative HPLC (23-43% acetonitrile in water /0.1% trifluoroacetic acid, 40 min). To the combined pure fractions are added 1 ml of 1 M aqueous hydrogen chloride and the mobile phase is removed by lyophilisation.

HPLC (A1): Rt = 29.14 min., 99 % (214 nm); HPLC (B1): Rt = 31.59 min., 100 % (214 nm);HPLC-MS: Rt = 4.37 min., (M+1) = 656, %Area by ELS = 100

Example 82

(*S,S*)-3-Amino-*N*-[5-(4-ethoxy-benzyl)-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-*N*-piperidin-4-ylmethyl-propionamide



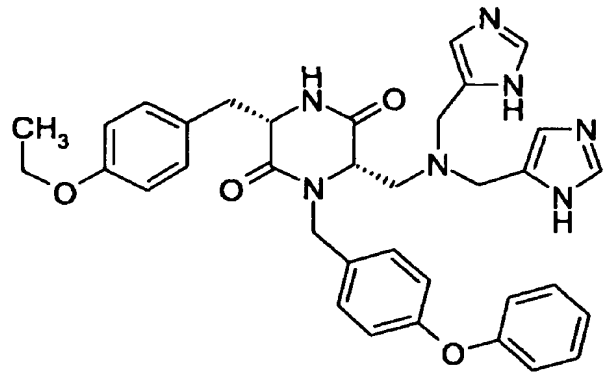
55 mg of the title compound is synthesized as described for (*S,S*)-3-amino-*N*-(1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-3-methyl-*N*-piperidin-4-ylmethyl-butyramide using 4-phenoxybenzaldehyde instead of biphenyl-4-carbaldehyde and (S)-2-*tert*-butoxycarbonylamino-3-(4-ethoxyphenyl)propionic acid instead of (S)-2-*tert*-butoxycarbonylamino-3-(2-naphtyl)propionic acid.

The title compound is purified by preparative HPLC (23-43% acetonitrile in water /0.1% trifluoroacetic acid, 40 min). To the combined pure fractions are added 1 ml of 1 M aqueous hydrogen chloride and the mobile phase is removed by lyophilisation.

HPLC (A1): Rt = 29.14 min., 99 % (214 nm); HPLC (B1): Rt = 31.59 min., 100 % (214 nm);HPLC-MS: Rt = 4.37 min., (M+1) = 656, %Area by ELS = 100

Example 83

(*S,S*)-6-{[Bis-(3*H*-imidazol-4-ylmethyl)-amino]-methyl}-3-(4-ethoxy-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione



Step A:

6.27 g of (S)-3-*tert*-butoxycarbonylamino-2-(4-phenoxybenzylamino)propionic acid methyl ester is synthesized as described for (2S)-2-[(biphenyl-4-ylmethyl)amino]-3-(9H-fluoren-9-ylmethoxycarbonylamino)propionic acid methyl ester using (S)-2-amino-3-*tert*-butoxycarbonylamino-propionic acid methyl ester instead of (S)-2-Amino-3-(9H-fluoren-9-ylmethoxycarbonylamino)propionic acid methyl ester.

HPLC-MS: Rt = 4.87 min., (M+1) = 401, %Area by ELS = 99

Step B:

To a solution of (S)-2-*tert*-butoxycarbonylamino-3-(4-ethoxyphenyl)propionic acid in 10 ml of dichloromethane is added O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (5.70 g, 15.0 mmol), 1-hydroxybezotriazole (2.04 g, 15.0 mmol) and N-ethyldiisopropylamin (2.57 ml, 15.0 mmol). Stirred for 20 min, after which a solution of (S)-3-*tert*-butoxycarbonylamino-2-(4-phenoxybenzylamino)propionic acid methyl ester (3.00 g, 7.49 mmol) in 10 ml of dichloromethane is added. Stirred overnight to give a yellow slurry. The mixture is diluted with 100 ml of dichloromethane and washed with 20 ml of aqueous sodium hydrogen sulfate (10%), 20 ml of aqueous sodium hydrogen carbonate (saturated), 20 ml of brine, dried over magnesium sulfate and filtered. Concentrated *in vacuo* to give a crude oil, which is purified by flash chromatography (100 g of SiO_2, heptane:ethyl acetate (7:3)) to afford 6.08 g (theoretically 7.49 mmol) of (2S)-3-*tert*-butoxycarbonylamino-2-[[(2S)-2-*tert*-butoxycarbonylamino-3-(4-ethoxyphenyl)propionyl]-(4-phenoxybenzyl)amino]propionic acid methyl ester as colorless oil.

Step C:

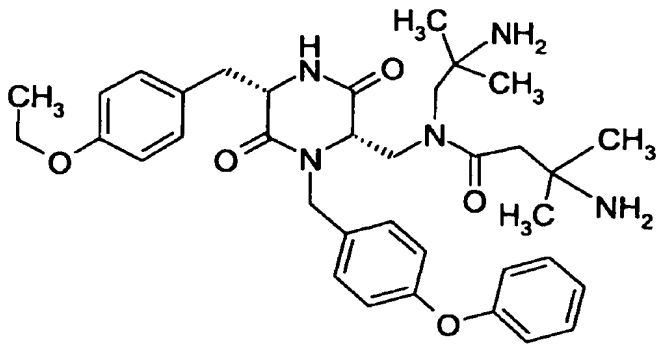
(2S)-3-*tert*-butoxycarbonylamino-2-[[(2S)-2-*tert*-butoxycarbonylamino-3-(4-ethoxyphenyl)propionyl]-(4-phenoxybenzyl)amino]propionic acid methyl ester (6.08 g, theoretically 7.49 mmol) is dissolved in 100 ml of dichloromethane and 100 ml of trifluoroacetic acid. Stirred for 2 hours, concentrated *in vacuo*, stripped 2 times from dichloromethane to give a thin orange oil. Dissolved in 100 ml of dichloromethane, 10 ml of N-ethyldiisopropylamin is added and the resulting mixture is stirred for 2 hours. Diluted with 100 ml of dichloromethane and 20 ml of aqueous sodium hydrogen carbonate (saturated), mixed and separated. The aqueous phase is extracted with 100 ml of dichloromethane, and the combined organic phases are washed with 20 ml of brine, dried over magnesium sulfate and filtered. Concentrated *in vacuo* to afford 5.19 g (theoretically 7.49 mmol) of (3S,6S)-(6-Aminomethyl-3-(4-ethoxybenzyl)-1-(4-phenoxybenzyl)piperazine-2,5-dione as yellow oil.
HPLC-MS: R_t = 4.80 min., (M+1) = 460, %Area by ELS = 89

Step D:

To a solution of 3S,6S)-(6-aminomethyl-3-(4-ethoxybenzyl)-1-(4-phenoxybenzyl)piperazine-2,5-dione (0.24 g, 0.35 mmol) in 10 ml of tetrahydrofuran and 10 ml of methanol is added 4(5)-imidazolecarboxaldehyde (0.10 g, 1.1 mmol), molecular sieves (4Å), acetic acid (42 µl, 0.20 mmol) and sodium cyanoborohydride (1.1 ml, 1.1 mmol). Stirred for 5 days. Filtered through Hyflo Super Cel®, concentrated *in vacuo* and purified by preparative HPLC (25-45% acetonitrile in water /0.1% trifluoroacetic acid, 40 min). The obtained pure fractions are combined and 2 ml of 1N aqueous hydrogen chloride is added. The compound is lyophilized to give 132 mg (52%) of the title compound as a hydrochloride-salt.
HPLC (A1): R_t = 29.27 min., 99 % (214 nm); HPLC (B1): R_t = 31.47 min., 98 % (214 nm);HPLC-MS: R_t = 4.40 min., (M+1) = 620, %Area by ELS = 100

Example 84

(*S,S*)-3-Amino-*N*-(2-amino-2-methyl-propyl)-*N*-[5-(4-ethoxy-benzyl)-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-3-methyl-butyramide



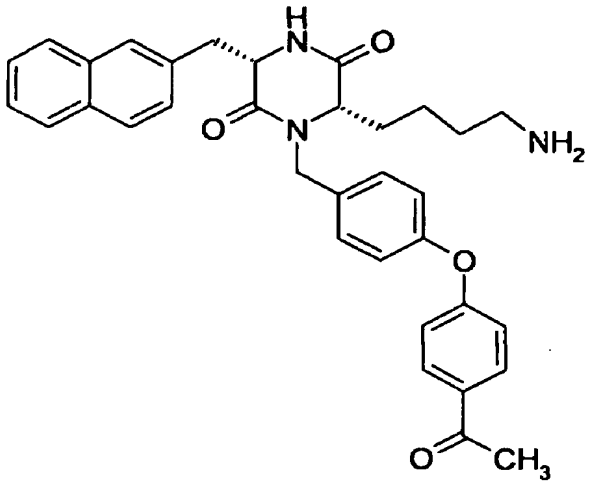
2.4 mg of the title compound is synthesized as described for (*S,S*)-3-amino-*N*-(1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-3-methyl-*N*-piperidin-4-ylmethyl-butyramide using 4-phenoxybenzaldehyde instead of biphenyl-4-carbaldehyde, (S)-2-*tert*-butoxycarbonylamino-3-(4-ethoxyphenyl)propionic acid instead of (S)-2-*tert*-butoxycarbonylamino-3-(2-naphtyl)propionic acid and (1,1-dimethyl-2-oxo-ethyl)carbamic acid *tert*-butyl ester instead of 4-formyl-piperidine-1-carboxylic acid *tert*-butyl ester.

The title compound is purified by preparative HPLC (23-43% acetonitrile in water/0.1% trifluoroacetic acid, 40 min). To the combined pure fractions are added 1 ml of 1 M aqueous hydrogen chloride and the mobile phase is removed by lyophilisation.

HPLC (h8): Rt = 9.09 min., 84 % (214 nm); HPLC-MS: Rt = 4.60 min., (M+1) = 630, %Area by ELS = 100

Example 85

(*S,S*)-1-[4-(4-Acetyl-phenoxy)-benzyl]-6-(4-amino-butyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



Step A:

To a solution of 4-hydroxybenzaldehyde (2.44 g, 20 mmol), triethylamine (3.37 ml, 24.2 mmol) and a catalytic amount of 4-dimethylaminopyridine in DCM (50 ml) is added a solution of *tert*-butyldimethylsilyl chloride in DCM (25 ml) dropwise during 30 min at 0 °C. The mixture is allowed to reach room temperature and stirred overnight. The mixture is evaporated *in vacuo* and the residue is purified on silica with ethyl acetate/heptane (1:4) to give the product, which is used in the next step.

HPLC-MS (Method C): *m/z* = 237 (M+1); R_t = 5.5 min.

Step B:

To a solution of H-Lys(Boc)-OMe HCl (3.0 g, 11.3 mmol) in THF (80 ml) is added the protected aldehyde from step A (2.66 g, 16.7 mmol) and *N,N*-diisopropylethylamine (2.0 ml, 11.3 mmol), and the mixture is stirred in the presence of powdered molecular sieves (4 Å) overnight at room temperature. Then methanol (10 ml), acetic acid (4.8 ml) and sodium cyanoborohydride (2.1 g, 34 mmol) is added and the mixture is stirred for 7 h at room temperature. The mixture is evaporated *in vacuo* and the residue is taken up in ethyl acetate (80 ml) and filtered. The filtrate is washed with 1N sodium hydroxide (60 ml), dried over sodium sulfate and evaporated to dryness *in vacuo* to give the crude product (5.97 g), which is used in the next step without further purification.

HPLC-MS (Method C): *m/z* = 481 (M+1); R_t = 3.6 min.

Step C:

To a solution of Boc-β-2-naphthyl-Ala-OH (2.0 g, 6.35 mmol) in THF (15 ml) is added *N,N'*-diisopropylcarbodiimide (0.49 ml, 3.17 mmol) and the mixture is stirred for 30 min at room temperature. A solution of the crude product from step B (1.52 g, ca. 3.1 mmol) in THF is added and the mixture is stirred for 4 h at room temperature. Then *N,N*-diisopropyl-ethylamine (1.1 ml, 6.4 mmol) is added and stirring is continued overnight. The mixture is evaporated *in vacuo* and the residue is taken up in ethyl acetate (50 ml) and washed successively with 1 N HCl (30 ml) and saturated aqueous sodium hydrogen carbonate (30 ml), dried over sodium sulfate and evaporated to dryness. Column chromatography on silica with ethyl acetate/heptane (1:2) afforded the intermediate in a yield of 1.10 g.

HPLC-MS (Method C): *m/z* = 800 (M+23); R_t = 7.0 min.

Step D:

A solution of the product from step C (1.1 g, 1.45 mmol) and TFA (10 ml) in DCM (25 ml) is stirred for 2 h at room temperature. After evaporation *in vacuo* the residue is taken up in toluene (20 ml) and the solvent is again removed *in vacuo*. The residue is now dissolved in DCM (25 ml) and *N,N*-diisopropylethylamine (1.0 ml, 5.8 mmol) is added. After stirring overnight, the mixture is evaporated *in vacuo* and the residue is taken up in ethyl acetate and stirred with 1 N HCl (20 ml) for 5 h at room temperature. After evaporation *in vacuo*, the residue is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1 %TFA in water and acetonitrile affording 364 mg of the ring-closed deprotected product.

HPLC-MS (Method C): *m/z* = 432 (M+1); R_t = 1.8 min.

Step E:

A solution of di-*tert*-butyl dicarbonate (203 mg, 0.93 mmol) and *N,N*-diisopropylethylamine (161 µl, 0.93 mmol) in DCM is added dropwise to a solution of the product from step D, and

the mixture is stirred overnight at room temperature. The mixture is evaporated *in vacuo* and the residue is purified on silica with ethyl acetate to give 365 mg of the Boc-protected product, which is used in the next step.

HPLC-MS (Method C): *m/z* = 554 (M+23); R_t = 3.8 min.

Step F:

A slurry of the product from step E (115 mg, 0.216 mmol), 4-acetylphenylboronic acid (177 mg, 1.08 mmol), copper(II) acetate (196 mg, 1.08 mmol), triethylamine (150 µl, 1.05 mmol) and powdered molecular sieves (4 Å) in THF is stirred at room temperature for about two days. The mixture is filtered and the filtrate is evaporated *in vacuo*. The product is isolated from the residue by column chromatography on silica with ethyl acetate/heptane (1:2) and used directly in the following step

HPLC-MS (Method C): *m/z* = 672 (M+23), 550 (M-100 +1); R_t = 4.7 min.

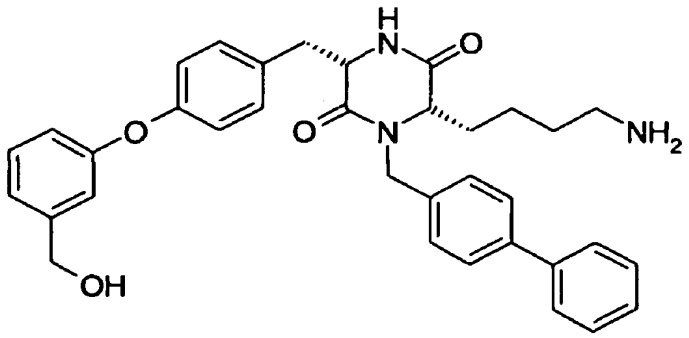
Step G:

The Boc-protected product from step F (100 mg, 0.15 mmol) is stirred with TFA (3 ml) in DCM (10 ml) for 1 h at room temperature. After evaporation *in vacuo*, the residual oil is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1 %TFA in water and acetonitrile. The product is dissolved in a mixture of 1 N HCl and methanol and evaporated *in vacuo* affording 364 mg of the title compound as the hydrochloride

HPLC-MS (Method C): *m/z* = 550 (M+1); R_t = 2.8 min

Example 86

(*S,S*)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(3-hydroxymethyl-phenoxy)-benzyl]-piperazine-2,5-dione



Step A:

288 mg of the boc-protected product of example **75** is dissolved in10 ml ethanol and 17 mg sodium borohydride is added. After a few hours (TLC control) the product is formed

and the solvent is removed *in vacuo*. Water is added and the mixture is extracted with ethyl acetate. The organic phase is dried over sodiumsulfate. The solvent is removed *in vacuo*and the residual is purified on silica with ethyl acetate.

Step B:

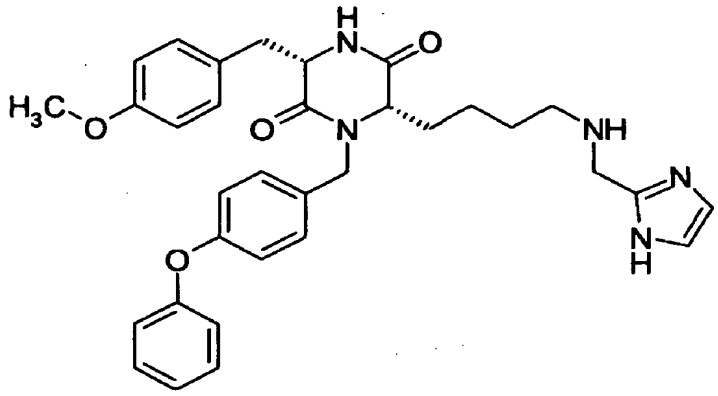
72 mg of the product from step A is dissolved in 10 ml dichlormethane and 1 ml trifluoroacetic acid is added. The mixture is stirred over night. The solvent is removed *in vacuo* and the residual is purified on a C18 reverse phase column.

^{1}H NMR ($CDCl_3$): δ 0.7-1.7 (6H, m), 2.7-3.3 (4H, m), 3.6-3.7 (1H, m), 3.85 (1H, d), 4.3-4.4 (1H, m), 4.5 (2H, s), 5.25 (1H, d), 6.7-7.6 (17H, m), 7.8-8.1 (2H, bs).

HPLC-MS (Method C): *m/z* = 564 (M+1); R_t = 2.96 min.

Example 87

(*S,S*)-6-{4-[(1*H*-Imidazol-2-ylmethyl)-amino]-butyl}-3-(4-methoxy-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione



Step A:

The product resin from general procedure C, step A, is used. To 0.18 g of this resin are added sequentially a solution of 0.468 mmol Boc-Lys(Fmoc)-OH in 1.6 ml of 1,2-dichloropropane / tetrahydrofuran (1:1), 0.045 ml (0.288 mmol) of diisopropylcarbodiimide, and a solution of 0.036 mmol of 4-dimethylamino pyridine in 0.2 ml of 1,2-dichloropropane. The mixture is shaken for 15 hours. The liquids are filtered off and the resin is washed with dimethylformamide (2x2 ml), tetrahydrofuran (2x2 ml), and dichloromethane (2x2 ml).

Step B:

The resin obtained by step A is shaken with a mixture of 2.5 ml trifluoroacetic acid/-dichloromethane 1:1 for one hour. The liquids are filtered off and the resin is washed with

tetrahydrofuran (2x2 ml), tetrahydrofuran / ethyldiisopropylamine 3:1 (3x2 ml), methanol (2 ml) and tetrahydrofuran (2 ml).

Step C:

To the resin obtained by step B, a solution of 0.36 mmol of 4-phenoxybenzaldehyde in 1.7 ml of 1-methyl-2-pyrrolidone and 0.1 ml of acetic acid are added. The mixture is shaken for three hours. The liquids are filtered off. The resin is shaken with a solution of 0.9 mmol of sodium cyanoborohydride in 1.7 ml of dichloromethane / methanol 1:1 for one hour. The liquids are filtered off. The resin is washed with methanol (2x2 ml), dichloromethane / methanol 1:1 (2 ml), dichloromethane / ethyldiisopropylamine 19:1 (2x2 ml), and tetrahydrofuran (2x2.5 ml).

Step D:

To the resin obtained by step C, a solution of 0.468 mmol of Boc-Tyr(Me)-OH in 1.6 ml of 1,2-dichloropropane / tetrahydrofuran 1:1 is added, followed by a solution of 0.288 mmol of diisopropylcarbodiimide in 0.2 ml of 1,2-dichloropropane. The mixture is shaken for 30 minutes. 0.043 ml (0.252 mmol) of ethyldiisopropylamine is added, and shaking is continued for 14 hours. The liquids are filtered off and the resin is washed with tetrahydrofuran (2x2.5 ml). The same amounts of Boc-Tyr(Me)-OH and diisopropylcarbodiimide as described above are added and the mixture is shaken for 45 minutes. 0.043 ml (0.252 mmol) of ethyldiisopropylamine is added, and shaking is continued for 7 hours. The liquids are filtered off and the resin is washed with dimethylformamide (2x2 ml) and tetrahydrofuran (2x3 ml).

Step E:

The resin obtained by step D is shaken with a mixture of 1.5 ml of dimethylformamide and 0.5 ml of piperidine for 30 min. The liquids are filtered off and the resin is washed with dimethylformamide (2x2 ml) and tetrahydrofuran (2x3 ml).

Step F:

To the resin obtained by step E, a suspension of 0.36 mmol of imidazole-2-carbaldehyde in 1.8 ml of 1-methyl-2-pyrrolidone / tetrahydrofuran 17:1 is added, followed by 0.1 ml of acetic acid. The mixture is shaken for 2.5 hours. The liquids are filtered off and the resin is washed with dichloromethane (4x2 ml). A solution of 0.90 mmol of sodium cyanoborohydride in 1.7 ml of dichloromethane / methanol 1:1 and 0.05 ml of acetic acid are added and the mixture is shaken for one hour. The liquids are filtered off and the resin is washed with methanol (2x2 ml), dichloromethane / methanol 1:1 (2 ml), tetrahydrofuran (2x3 ml), dichloromethane / ethyldiisopropylamine 8:1 (2x1.8 ml), and dichloromethane (5x2 ml).

Step G:

The resin obtained by step F is shaken with 2.5 ml of dichloromethane / trifluoroacetic acid 1:1 for 30 minutes. The liquids are filtered off and the resin is washed with dichloromethane (2x2 ml), tetrahydrofuran (2x2.5 ml), and methanol (2x2.5 ml).

Step H:

To the resin obtained by step G, 2.0 ml of dichloromethane and 1.0 ml of 40% methylamine in methanol are added. The mixture is shaken for 3.5 hours. The mixture is filtered and the filtrate is collected. The resin is washed with 3.5 ml of dichloromethane / methanol 6:1 and the washing filtrate is collected. Both filtrates are mixed and evaporated to give a residue.

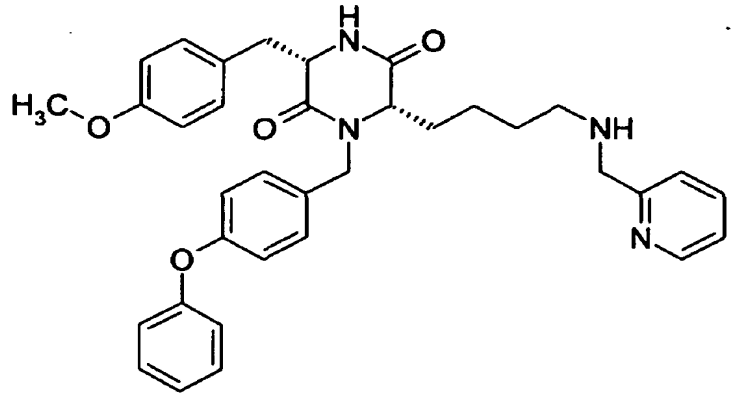
Step I:

The residue obtained by step H is dissolved in a mixture of 4.8 ml of water, 3.2 ml of acetonitrile and 0.8 ml of 1M aqueous hydrochloric acid and purified by HPLC. Addition of dilute aqueous hydrochloric acid and freeze-drying afforded 12.2 mg of the product.

HPLC-MS (Method B): *m/z* = 568 (M+1); R_t = 4.67 min.

Example 88

(*S,S*)-3-(4-Methoxy-benzyl)-1-(4-phenoxy-benzyl)-6-{4-[(pyridin-2-ylmethyl)-amino]-butyl}-piperazine-2,5-dione



Steps A-H:

The same procedure as described for example **87**, steps A-H, is performed. In step F, a solution of pyridine-2-carbaldehyde is used instead of the imidazole-2-carbaldehyde suspension.

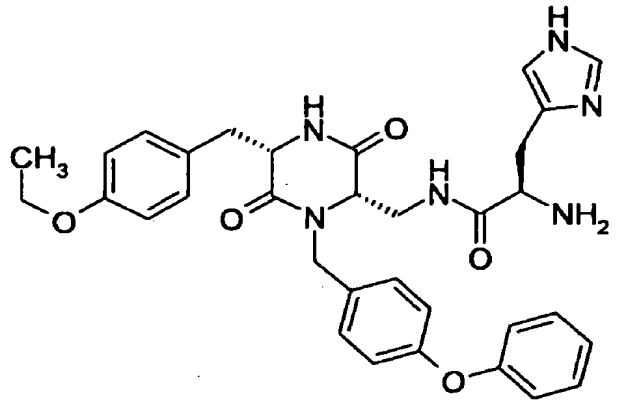
Step I:

The residue obtained by step H is dissolved in a mixture of 4.8 ml water, 3.2 ml of acetonitrile and 0.8 ml of 1M aqueous hydrochloric acid and purified by HPLC. Addition of dilute aqueous hydrochloric acid and freeze-drying afforded 20.6 mg of the product.

HPLC-MS (Method B): *m/z* = 579 (M+1); R_t = 4.97 min.

Example 89

(2*R*,2'*S*,5'*S*)-2-Amino-*N*-[5-(4-ethoxy-benzyl)-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-3-(1*H*-imidazol-4-yl)-propionamide



Step A:

To a solution of (1R)-4-(2-*tert*-butoxycarbonylamino-2-carboxyethyl)imidazole-1-carboxylic acid *tert*-butyl ester (0.35 mmol) in 1 ml of dichloromethane is added O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetrametyluronium hexafluorophosphate (0.13, 0.35 mmol, 1-hydroxybenzo-triazole (0.048 g, 0.35 mmol) and N-ethyldiisopropylamin (120 µl, 0.70 mmol). Stirred for 20 min, after which a solution of (S3S,6S)-(6-aminomethyl-3-(4-ethoxybenzyl)-1-(4-phenoxy-benzyl)piperazine-2,5-dione (0.24 g, 0.35 mmol) in 1 ml of dichloromethane is added. Stirred overnight to give a yellow solution. Diluted with 15 ml of dichloromethane, washed with 2.5 ml of aqueous sodium hydrogen sulfate (10%), 2.5 ml of aqueous sodium hydrogen carbonate (saturated), 2.5 ml of brine, dried over magnesium sulfate and filtered. Concentrated *in vacuo* to afford 0.33 g (theoretically 0.35 mmol) of 4-(2-*tert*-butoxycarbonyl-amino-2-(1R)-{[(2S,5S)-5-(4-ethoxybenzyl)-3,6-dioxo-1-(4-phenoxybenzyl)piperazin-2-ylmethyl] carbamoyl}ethyl)imidazole-1-carboxylic acid *tert*-butyl ester as yellow oil.

HPLC-MS: Rt = 6.53 min., (M+1) = 797, %Area by ELS = 70

Step B:

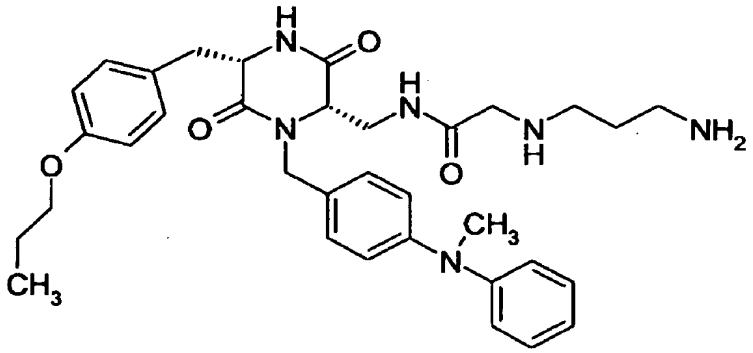
To a solution of -(1R)-{[(2S,5S)-5-(4-ethoxybenzyl)-3,6-dioxo-1-(4-phenoxybenzyl)piperazin-2-ylmethyl]carbamoyl}ethyl)imidazole-1-carboxylic acid *tert*-butyl ester (theoretically 0.35

mmol) in 5 ml of dichloromethane is added 5 ml of trifluoroacetic acid. Stirred for 2 hours, concentrated *in vacuo* and purified by preparative HPLC (23-43% acetonitrile in water /0.1% trifluoroacetic acid, 40 min). To the combined pure fractions are added 2 ml of 1 M aqueous hydrogen chloride and the mobile phase is removed by lyophilisation to afford 88.1 mg of the title compound.

HPLC (A1): Rt = 29.68 min., 100 % (214 nm); HPLC (B1): Rt = 31.84 min., 100 % (214 nm);HPLC-MS: Rt = 4.33 min., (M+1) = 597, %Area by ELS = 100

Example 90

(*S,S*)-2-(3-Amino-propylamino)-*N*-[1-[4-(methyl-phenyl-amino)-benzyl]-3,6-dioxo-5-(4-propoxy-benzyl)-piperazin-2-ylmethyl]-acetamide



Step A:

0.5 g (2.0 mmol) H-Dap(Boc)-OMe hydrochloride and 0.4 g 4-(methyl-phenyl-amino)-benzaldehyde are taken up in 20 ml THF. 340 µl DIPEA is added and the mixture is stirred over night. 0.4 g $NaCNBH_3$, 2 ml methanol and 1 ml HOAc are added and the mixture is stirred for 5 h. The solvent is removed *in vacuo* and the residual oil is taken up in 75 ml ethyl acetate. The org. phase is washed twice with 50 ml 1N NaOH and dried over sodium sulfate. The solvent is removed *in vacuo* and the crude material is used for the next step.

Step B:

1.4 g (3.9 mmol) Boc-Tyr(tBu)-OH are dissolved in 20 ml THF. 300 µl diisopropylcarbodiimide are added and the the mixture is stirred for 1 h. The crude product from step A is added in 10 ml THF. After 2.5 h 320 µl DIPEA is added and the reaction is stirred over night. Another 320 µl DIPEA are added and after 1 h the solvent is removed *in vacuo*. The residual oil is taken up in 50 ml ethyl acetate. The org. phase is washed twice with 50 ml 1N HCl, twice with 50 ml sat. sodium hydrogen carbonate and dried over sodium

sulfate. The solvent is removed *in vacuo* and the residual oil is purified on silica using ethyl acetate/heptane 2:3.

Step C:

0.5 g (0.8 mmol) of the product from step B is dissolved in 15 ml dichlormethane and 15 ml TFA. The solvent is removed after 30 min and the residual oil is dissolved in 25 ml dichlormethane and 2 ml DIPEA. The solvent is removed after 45 min and the oil is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

Step D:

0.3 g (0.7 mmol) of the product from step C is dissolved in 15 ml dichlormethane. 290 µl Boc-anhydrid and 115 µl DIPEA are added. The mixture is stirred over night. The solvent is removed *in vacuo* and the oil is purified on silica with ethyl acetate.

Step E:

0.2 g (0.4 mmol) of the product from step D is dissolved in 5 ml THF. 0.14 g (1.5 equi.) triphenylphosphine and 41 µl 1-propanol are added. 87 µl diethylazadicarboxylate is added and the mixture is stirred over night. 0.10 g (1 equi) triphenylphosphine, 28 µl 1-propanol and 58 µl diethylazadicarboxylate are added again and the reaction is stirred for a second night. The solvent is removed *in vacuo* and the oil is purified on a C18 reverse phase column (Sep-Pak, Waters, 10 g) with 0.1% TFA in water and acetonitril.

Step F:

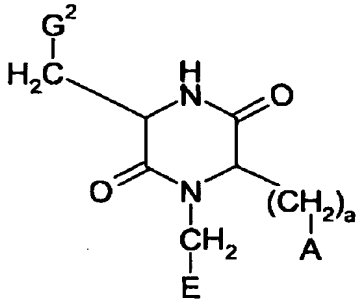
0.22 g (0.4 mmol) of the product from step E is dissolved in 10 ml dichlormethane and 10 ml TFA. The solvent is removed *in vacuo* after 25 min.

HPLC-MS (Method C): *m/z* = 601 (M+1); R_t = 2.77 min.

Examples 91 to 102

Compounds of general formula (If) is synthesised on a small shaker according to general procedure C using as first building block (step B) Fmoc-L-Lys(Boc)-OH. 3-Phenoxy-benzaldehyde, biphenyl-4-carbaldehyde, benzaldehyde or 4-benzyloxy-benzaldehyde is used as second building block (step D). The third building block (step E) is covered by Boc-β-(2-naphthyl)-L-Ala-OH, Boc-L-Tyr(bz)-OH, Boc-L-Trp(Boc)-OH, Boc-β-(1-naphthyl)-L-Ala-OH, Boc-L-Bip-OH or Boc-L-Phe-OH, samples are analysed using HPLC-MS method D.

Examples of compounds prepared according to said procedure of the general formula (If) are shown in Table VIII.



Formula (If)

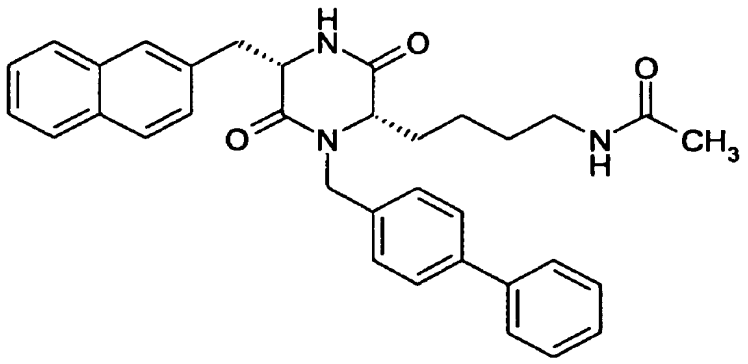
Table VIII

Example #	a	A	E	G^2	*Stereo pos 3*	*Stereo pos 6*	Purity by ELS
91	4	$-NH_2$	-3-PhOPh	-2-Np	*S*	*S*	76%
92	4	$-NH_2$	-3-PhOPh	-Ph(4-OBzl)	*S*	*S*	67%
93	4	$-NH_2$	-3-PhOPh	-1-Np	*S*	*S*	74%
94	4	$-NH_2$	-3-PhOPh	-4-Biph	*S*	*S*	76%
95	4	$-NH_2$	-4-Biph	-2-Np	*S*	*S*	85%
96	4	$-NH_2$	-4-Biph	-Ph(4-OBzl)	*S*	*S*	75%
97	4	$-NH_2$	-4-Biph	-1-Np	*S*	*S*	80%
98	4	$-NH_2$	-4-Biph	-4-Biph	*S*	*S*	73%
99	4	$-NH_2$	-Ph(4-OBzl)	-2-Np	*S*	*S*	76%
100	4	$-NH_2$	-Ph(4-OBzl)	-Ph(4-OBzl)	*S*	*S*	73%
101	4	$-NH_2$	-Ph(4-OBzl)	-1-Np	*S*	*S*	76%
102	4	$-NH_2$	-Ph(4-OBzl)	-4-Biph	*S*	*S*	75%

Stereo pos 3 and 6 = Absolute stereochemistry at the position 3 and 6, respectively, of the diketopiperazin ring system

Example 103

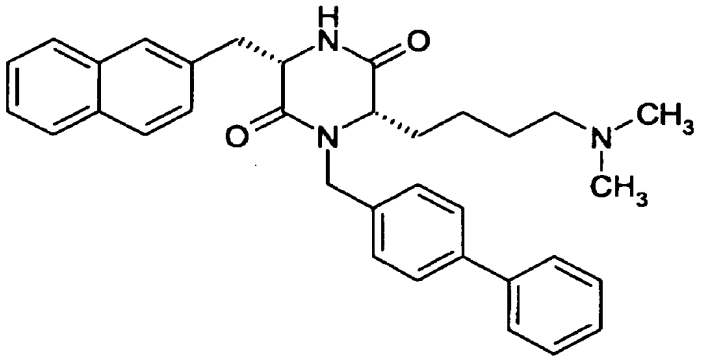
N-[4-((2S,5S)-1-Biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-yl)-butyl]-acetamide



To the corresponding product of general procedure E, step G (196 mg, 0.4 mmol) and acetic anhydride (0.042 ml, 0.44 mmol) in dichloromethane (5 ml) is added at room temperature N-ethyldiisopropylamine (0.1 ml, 0.8 mmol) and the mixture is stirred for 1 h. Flash chromatography (silica, dichloromethane / MeOH 30:1 → 20:1) gave the product (188 mg, 88%). ESI-MS: $(M+H)^+$ = 534.

Example 104

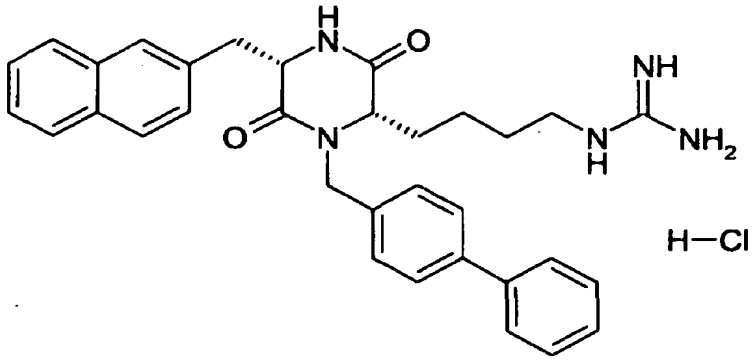
(3S,6S)-1-Biphenyl-4-ylmethyl-6-(4-dimethylamino-butyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



To the corresponding product of general procedure E, step G (245 mg, 0.5 mmol) and formaldehyde (37% in water, 0.67 ml, 8.9 mmol) in MeOH (10 ml) is added in portions sodium borohydride (151 mg, 4 mmol) and the mixture is stirred at room temperature overnight. Sat aq. sodium bicarbonate (40 ml) is added and the mixture is extracted with dichloromethane (3x70 ml). The combined org. layers are dried over sodium sulfate and purified by flash chromatography (silica, dichloromethane / MeOH 20:1 + 1% conc. aq. ammonia) to give the product (72 mg, 28%). ESI-MS: $(M+H)^+$ = 520.

Example 105

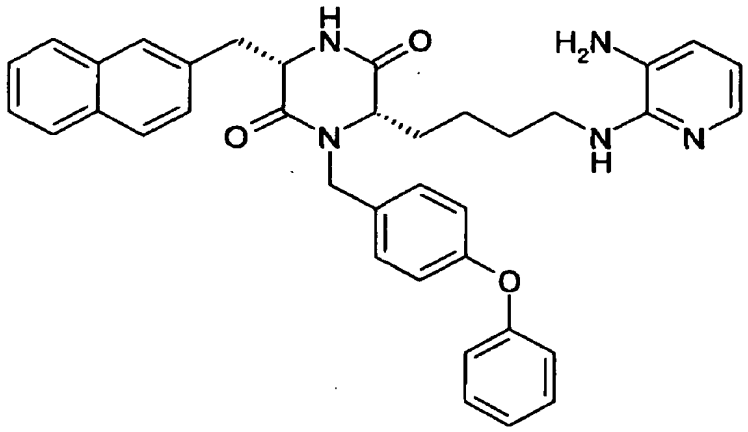
N-[4-((2S,5S)-1-Biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-yl)-butyl]-guanidine hydrochloride



To the corresponding product of general procedure E, step G (196 mg, 0.4 mmol) in DMF (5 ml) is added pyrazole-1-carboxamidine hydrochloride (60 mg, 0.41 mmol) and the mixture is stirred at room temperature overnight. Ether is added and the white precipitate collected by filtration. The precipitate is washed repeatedly with ether and dried under high vacuum to give the product (186 mg, 82%). ESI-MS: $(M+Cl)^-$ = 570.

Example 106

(3S,6S)-6-[4-(3-Amino-pyridin-2-ylamino)-butyl]-3-naphthalen-2-ylmethyl-1-(4-phenoxy-benzyl)-piperazine-2,5-dione



Step 1:

To the corresponding product of general procedure E, step G (100 mg, 0.2 mmol) and 2-chloro-3-nitro-pyridine (40 mg, 0.25 mmol) in DMF (1 ml) is added N-ethyldiisopropyl-amine (0.07 ml, 0.4 mmol) and the mixture is stirred at room temperature for 72 h. The mixture is diluted with ice water (50 ml) and the precipitate is collected by filtration. Flash

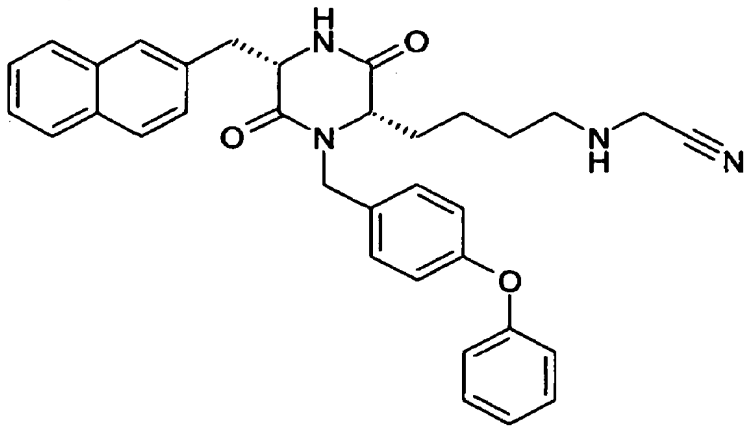
chromatography (silica, dichloromethane / MeOH 30:1) gave the corresponding 3-nitropyridyl intermediate (90 mg, 73%). ESI-MS: $(M+H)^+$ = 630

Step 2:

The 3-nitropyridyl intermediate (0.14 mmol) is hydrogenated (50 psi) in MeOH (15 ml) in the presence of Raney nickel (100 mg) at room temperature for 1 h. The catalyst is removed by filtration and the filtrate concentrated *in vacuo*. The residue is dissolved in ether (10 ml) and the product precipitated by addition of HCl (6-7 N in isopropanol) to give the product (38%). ESI-MS: $(M+H)^+$ = 600.

Example 107

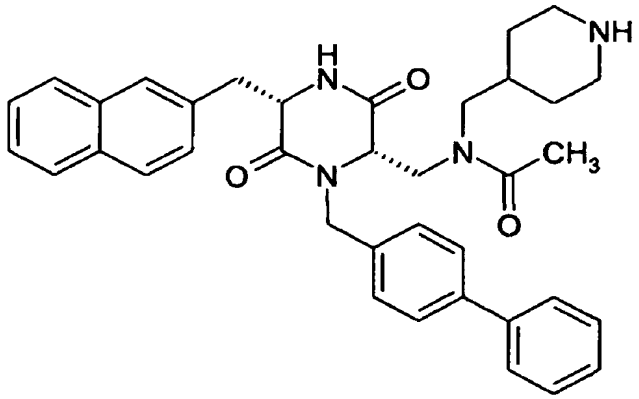
{4-[(2S,5S)-5-Naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-yl]-butylamino}-acetonitrile



The corresponding product of general procedure E, step G (150 mg, 0.295 mmol) and chloroacetonitrile (0.02 ml, 0.313 mmol) in EtOH (1.5 ml) is heated to reflux for 3 h. Chloroacetonitril (0.01 ml) is added and the mixture is heated for another 2 h. The mixture is concentrated *in vacuo* and the residue purified by flash chromatography (silica, dichloro-methane / MeOH 20:1) to give the product (80 mg, 50%). ESI-MS: $(M+H)^+$ = 547

Example 108

N-((2S,5S)-1-Biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-acetamide



Step 1:

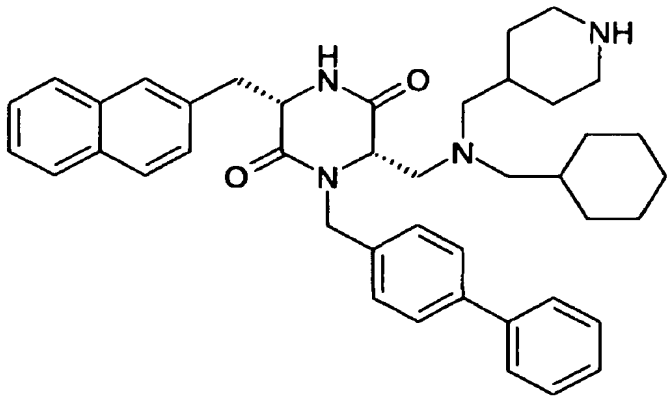
To the Cbz-protected corresponding product from general procedure G, step D (300 mg, 0.44 mmol) and acetic anhydride (0.085 ml, 0.90 mmol) is added at room temperature N-ethyldiisopropylamine (0.25 ml) and the mixture is stirred for 4 h. Sat. aq. sodium bicarbonate is added and the mixture is extracted with dichloromethane (3x50 ml). The combined org. layer are dried over sodium sulfate and purified by flash chromatography (silica, dichloromethane/MeOH 20:1) to give the acylated intermediate (300 mg, 94%). ESI-MS: $(M+H)^+$ = 723.

Step 2:

The acylated intermediate (290 mg, 0.40 mmol) in MeOH (30 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1 h. The catalyst is removed by filtration and the filtrate concentrated *in vacuo*. The residue is triturated (dichloromethane / ether) to give the product (112 mg, 47%). ESI-MS: $(M+H)^+$ = 589.

Example 109

(3S,6S)-1-Biphenyl-4-ylmethyl-6-[(cyclohexylmethyl-piperidin-4-ylmethyl-amino)-methyl]-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



Step 1:

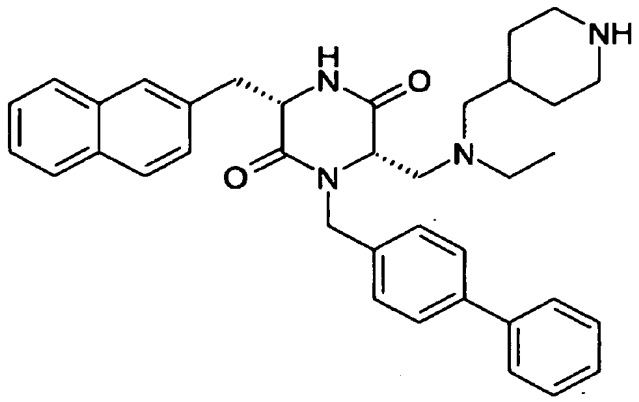
To the corresponding Cbz-protected product from general procedure G, step D (300 mg, 0.44 mmol) and cyclohexanecarboxaldehyde (0.12 ml, 0.99 mmol) in THF (20 ml) is added glacial acetic acid (0.06 ml) and the mixture is stirred for 1 h. Sodium triacetoxyborohydride (240 mg, 1.076 mmol) is added and the mixture is stirred for 3 days. Sat. aq. sodium bicarbonate is added, the mixture stirred for 30 min., and then extracted with ether (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloromethane/MeOH 30:1) to give the Cbz-protected intermediate (260 mg, 76%). ESI-MS: $(M+H)^+ = 777$.

Step 2:

The Cbz-protected intermediate (250 mg, 0.322 mmol) in MeOH (30 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The residue is triturated (dichloromethane/ether) to give the product (125 mg, 60%). ESI-MS: $(M+H)^+ = 643$.

Example 110

(3S,6S)-1-Biphenyl-4-ylmethyl-6-[(ethyl-piperidin-4-ylmethyl-amino)-methyl]-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



Step 1:

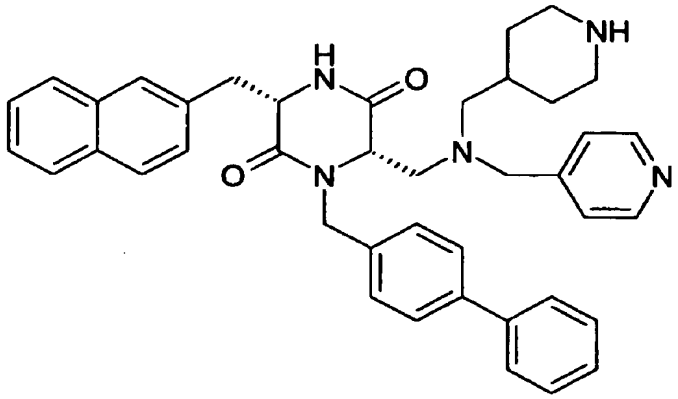
To the corresponding Cbz-protected product from general procedure G, step D (300 mg, 0.44 mmol) and acetaldehyde (100 mg, 2.27 mmol) in THF (20 ml) is added glacial acetic acid (0.06 ml) and the mixture is stirred for 1 h. Sodium triacetoxyborohydride (240 mg, 1.076 mmol) is added and the mixture is stirred for 3 days. Sat. aq. sodium bicarbonate is added, the mixture stirred for 30 min., and then extracted with ether (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloromethane/MeOH 30:1) to give the Cbz-protected intermediate (180 mg, 58%). ESI-MS: $(M+H)^+$ = 709.

Step 2:

The Cbz-protected intermediate (250 mg, 0.322 mmol) in MeOH (30 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The residue is triturated (dichloromethane / ether) to give the product (56 mg, 41%). ESI-MS: $(M+H)^+$ = 575.

Example 111

(3S,6S)-1-Biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-6-[(piperidin-4-ylmethyl-pyridin-4-ylmethyl-amino)-methyl]-piperazine-2,5-dione



Step 1:

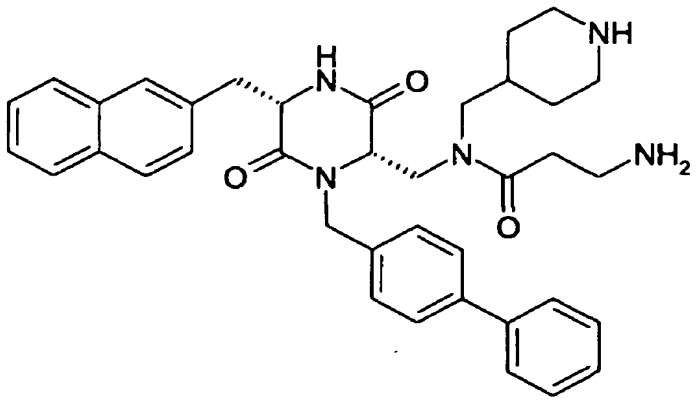
To the corresponding Cbz-protected product from general procedure G, step D (300 mg, 0.44 mmol) and 4-pyridylcarbaldehyde (100 mg, 0.934 mmol) in THF (20 ml) is added glacial acetic acid (0.06 ml) and the mixture is stirred for 1 h. Sodium triacetoxyborohydride (240 mg, 1.076 mmol) is added and the mixture is stirred for 3 days. Another portion of 4-pyridinecarboxaldehyde (100 mg, 0.934 mmol), glacial acetic acid (0.06 ml), and sodium triacetoxyborohydride (240 mg, 1.076 mmol) is added and the mixture is stirred for another 2 days. Sat. aq. sodium bicarbonate is added, the mixture stirred for 30 min., and then extracted with ethyl acetate (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, di-chloromethane / MeOH 20:1) to give the Cbz-protected intermediate (260 mg, 76%). ESI-MS: $(M+H)^+$ = 772.

Step 2:

The Cbz-protected intermediate (230 mg, 0.298 mmol) in MeOH (30 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 2 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. Flash chromatography (alumina (activity II-III), dichloromethane / MeOH 10:1 → 5:1) gave the product (85 mg, 45%). ESI-MS: $(M+H)^+$ = 638.

Example 112

3-Amino-N-((2S,5S)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-propionamide



Step 1:

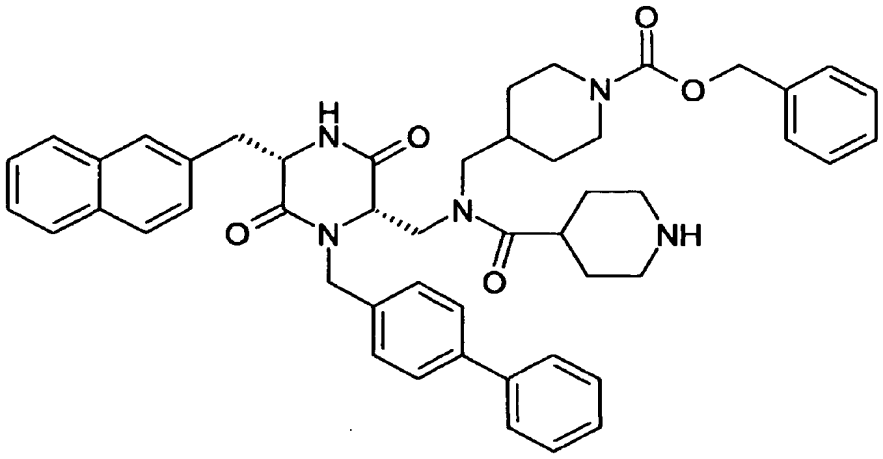
To the corresponding Cbz-protected product from general procedure G, step D (240 mg, 0.353 mmol), 3-N-Cbz-aminopropionic acid (240 mg, 1.075 mmol), HOBt (140 mg, 1.034 mmol), and TBTU (340 mg, 1.06 mmol) in THF (15 ml) is added at room temperature N-ethyl-diisopropylamine (0.2 ml, 1.148 mmol) and the mixture is stirred overnight. Sat. aq. sodium bicarbonate (40 ml) is added, the mixture stirred for 30 min., and then extracted with dichloromethane (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloromethane/MeOH 20:1) to give the bis-Cbz-protected intermediate (287 mg, 92%). ESI-MS: $(M+H)^+$ = 886.

Step 2:

The Cbz-protected intermediate (272 mg, 0.308 mmol) in MeOH (40 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 2 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. Trituration (dichloromethane / ether) of the residue gave the product (115 mg, 60%). ESI-MS: $(M+H)^+$ = 618.

Example 113

4-{[((2S,5S)-1-Biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-(piperidine-4-carbonyl)-amino]-methyl}-piperidine-1-carboxylic acid benzyl ester



Step 1:

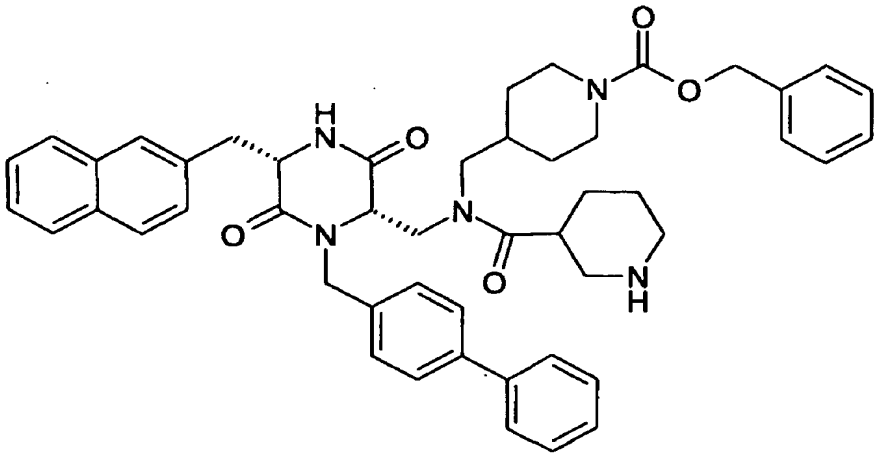
To the corresponding Cbz-protected product from general procedure G, step D (300 mg, 0.441 mmol), N-Boc-piperidin-4-yl carboxylic acid (125 mg, 0.545 mmol), HOBT (70 mg, 0.517 mmol), and TBTU (170 mg, 0.529 mmol) in THF (15 ml) is added at room temperature N-ethyldiisopropylamine (0.1 ml, 0.57 mmol) and the mixture is stirred overnight. Sat. aq. sodium bicarbonate (40 ml) is added, the mixture stirred for 15 min., and then extracted with dichloromethane (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloromethane/MeOH 20:1) to give the bis-protected intermediate (120 mg, 31%). ESI-MS: $(M+H)^+$ = 892.

Step 2:

To the bis-protected intermediate (270 mg, 0.303 mmol) in dichloromethane (5 ml) is added at room temperature TFA (0.5 ml) and the mixture is stirred for 2.5 h. Sat. aq. sodium bicarbonate is added, the mixture is stirred for 15 min., and then extracted with dichloromethane (3x80 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (alumina (activity II-III), dichloromethane/MeOH 20:1 → 10:1) to give the Cbz-protected product (185 mg, 77%). ESI-MS: $(M+H)^+$ = 792.

Example 114

4-{[((2S,5S)-1-Biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-((RS)-piperidine-3-carbonyl)-amino]-methyl}-piperidine-1-carboxylic acid benzyl ester



Step 1:

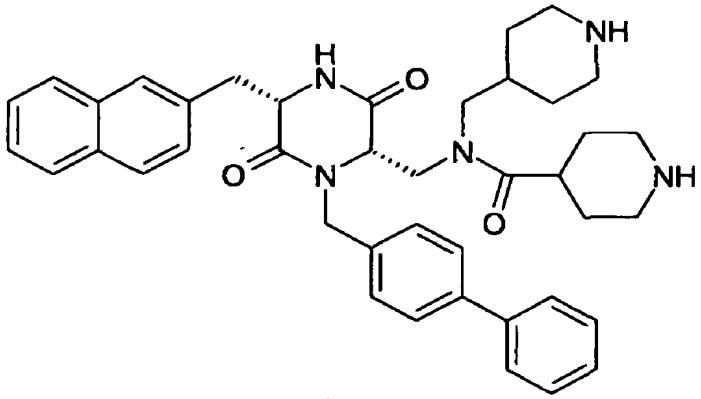
To the corresponding Cbz-protected product from general procedure G, step D (300 mg, 0.441 mmol), N-Boc-piperidin-3-yl carboxylic acid (125 mg, 0.545 mmol), HOBT (70 mg, 0.517 mmol), and TBTU (170 mg, 0.529 mmol) in THF (15 ml) is added at room temperature N-ethyldiisopropylamine (0.1 ml, 0.57 mmol) and the mixture is stirred for 3 days. Sat. aq. sodium bicarbonate (40 ml) is added, the mixture stirred for 15 min., and then extracted with dichloromethane (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloromethane/MeOH 20:1) to give the bis-protected intermediate (184 mg, 47%). ESI-MS: $(M+H)^+$ = 892.

Step 2:

To the bis-protected intermediate (176 mg, 0.197 mmol) in dichloromethane (5 ml) is added at room temperature TFA (0.5 ml) and the mixture is stirred for 3 h. Sat. aq. sodium bicarbonate is added, the mixture is stirred for 15 min., and then extracted with dichloromethane (3x80 ml). The combined org. layers are dried over sodium sulfate and concentrated *in vacuo*. Trituration (dichloromethane / ether) gave the Cbz-protected product (88 mg, 56%). ESI-MS: $(M+H)^+$ = 792.

Example 115

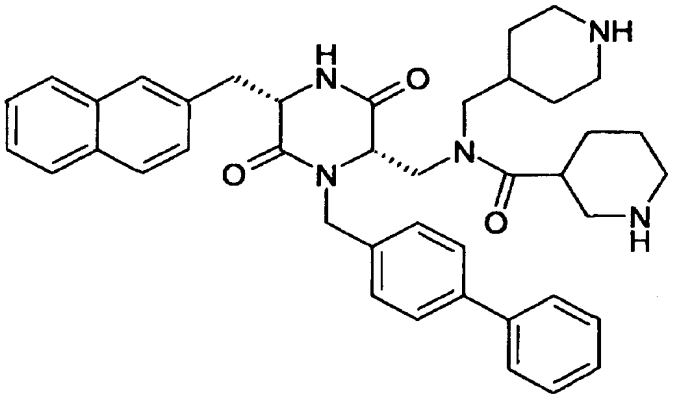
Piperidine-4-carboxylic acid ((2S,5S)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-piperidin-4-ylmethyl-amide



The Cbz-protected precursor from example **113** (170 mg, 0.215 mmol) in MeOH (30 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1.5 h. The catalyst is removed by filtration and the filtrate concentrated *in vacuo*. The residue is triturated (dichloro-methane / ether) to give the product (110 mg, 78%). ESI-MS: $(M+H)^+$ = 658.

Example 116

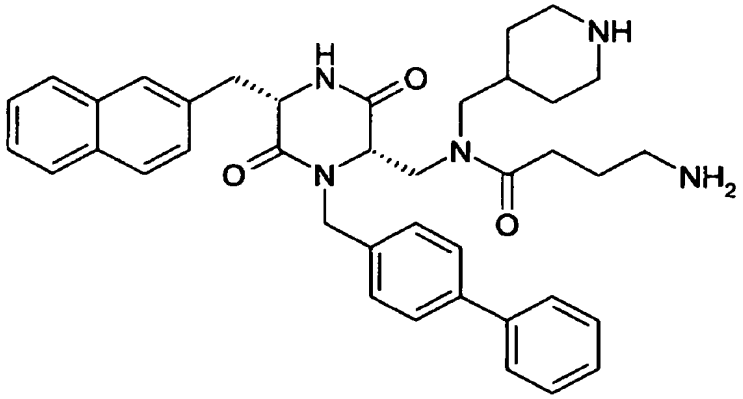
(RS)-Piperidine-3-carboxylic acid ((2S,5S)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-piperidin-4-ylmethyl-amide



The Cbz-protected precursor from example 114 (77 mg, 0.097 mmol) in MeOH (20 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1.5 h. The catalyst is removed by filtration and the filtrate concentrated *in vacuo*. The residue is triturated (dichloro-methane / ether) to give the product (44 mg, 69%). ESI-MS: $(M+H)^+$ = 658.

Example 117

4-Amino-N-((2S,5S)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-butyramide



Step 1:

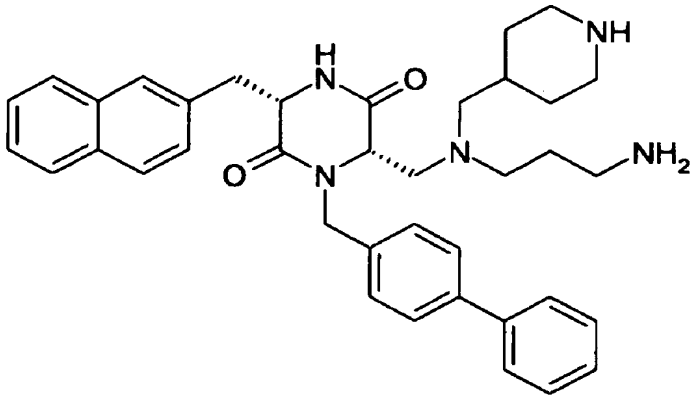
To the corresponding Cbz-protected product from general procedure G, step D (240 mg, 0.353 mmol), 4-N-Cbz-aminobutyric acid (240 mg, 1.012 mmol), HOBt (140 mg, 1.034 mmol), and TBTU (340 mg, 1.034 mmol) in THF (20 ml) is added at room temperature N-ethyldiisopropylamine (0.1 ml, 0.57 mmol) and the mixture is heated to reflux for 6 h. Sat. aq. sodium bicarbonate (40 ml) is added, the mixture stirred for 15 min., and then extracted with dichloromethane (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloromethane/MeOH 20:1) to give the bis-Cbz-protected intermediate (160 mg, 50%). ESI-MS: $(M+H)^+$ = 900.

Step 2:

The bis-Cbz-protected intermediate (160 mg, 0.178 mmol) in MeOH (30 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1.5 h. The catalyst is removed by filtration and the filtrate concentrated *in vacuo*. The residue is triturated (dichloromethane / ether) to give the product (80 mg, 71%). ESI-MS: $(M+H)^+$ = 632.

Example 118

(3S,6S)-6-{[(3-Amino-propyl)-piperidin-4-ylmethyl-amino]-methyl}-1-biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



Step 1:

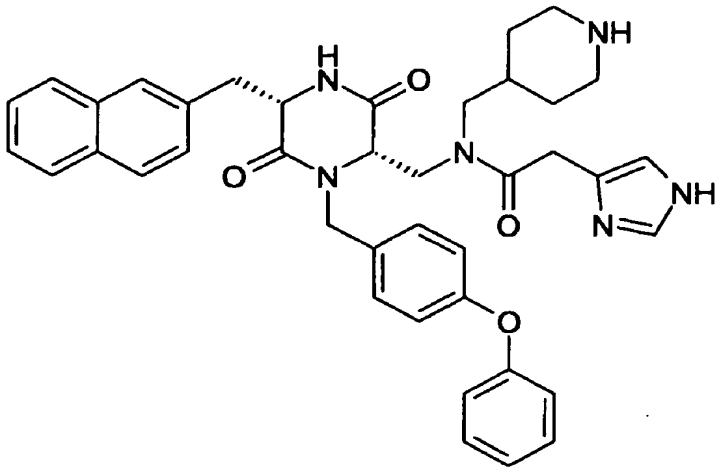
To the corresponding Cbz-protected product from general procedure G, step D (400 mg, 0.588 mmol) and 3-N-Cbz-propionaldehyde (250 mg, 1.146 mmol) in THF (20 ml) is added glacial acetic acid (0.06 ml) and the mixture is stirred for 1 h. Sodium triacetoxyborohydride (300 mg, 1.345 mmol) is added and the mixture is stirred for 3 days. Sat. aq. sodium bicarbonate is added, the mixture stirred for 30 min., and then extracted with ether (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloromethane/MeOH 30:1) to give the bis-Cbz-protected intermediate (450 mg, 88%). ESI-MS: $(M+H)^+$ = 872.

Step 2:

The Cbz-protected intermediate (440 mg, 0.505 mmol) in MeOH (40 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1.5 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The residue is triturated (dichloromethane/ether) to give the product (154 mg, 51%). ESI-MS: $(M+H)^+$ = 604.

Example 119

1H-Imidazole-4-carboxylic acid [(2S,5S)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-piperidin-4-ylmethyl-amide



Step 1:

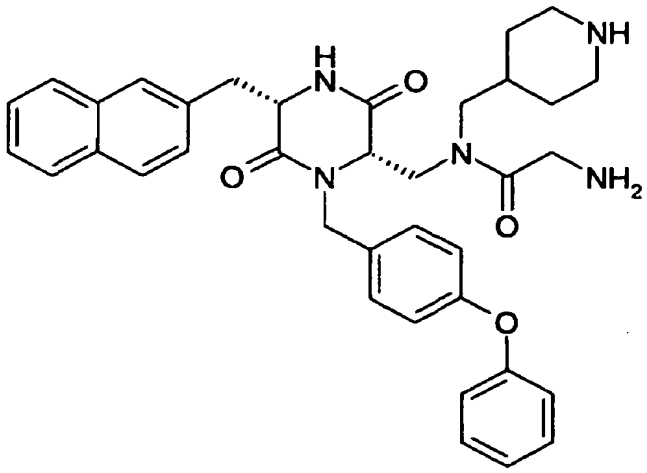
To the corresponding Cbz-protected product from general procedure G, step D (225 mg, 0.323 mmol), 4-imidazole-acetic acid (170 mg, 1.046 mmol), HOBT (140 mg, 1.034 mmol), and TBTU (340 mg, 1.06 mmol) in THF (15 ml) is added at room temperature N-ethyl-diisopropylamine (0.4 ml, 2.296 mmol) and the mixture is stirred for 6 h. Sat. aq. sodium bicarbonate (40 ml) is added, the mixture stirred for 30 min., and then extracted with ethyl acetate (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (alumina (activity II-III), dichloro-methane/MeOH 20:1 → 8:1) to give the Cbz-protected intermediate (100 mg, 38%). ESI-MS: $(M+H)^+$ = 805.

Step 2:

The Cbz-protected intermediate (100 mg, 0.124 mmol) in MeOH (20 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. Trituration (dichloromethane/-ether) of the residue gave the product (46 mg, 55%). ESI-MS: $(M+H)^+$ = 671.

Example 120

2-Amino-N-[(2S,5S)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-N-piperidin-4-ylmethyl-acetamide



Step 1:

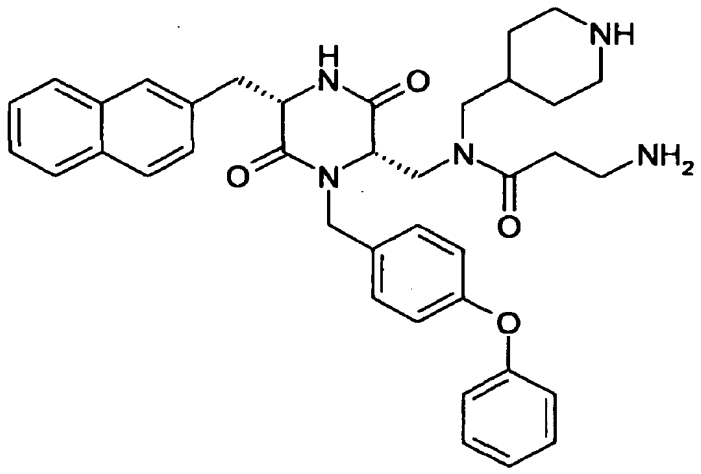
To the corresponding Cbz-protected product from general procedure G, step D (225 mg, 0.323 mmol), N-Cbz-glycine (220 mg, 1.052 mmol), HOBT (140 mg, 1.034 mmol), and TBTU (340 mg, 1.06 mmol) in THF (15 ml) is added at room temperature N-ethyldiisopropyl-amine (0.2 ml, 1.148 mmol) and the mixture is stirred overnight. Sat. aq. sodium bicarbonate (40 ml) is added, the mixture stirred for 30 min., and then extracted with ether (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloromethane/MeOH 20:1) to give the Cbz-protected intermediate (184 mg, 64%). ESI-MS: $(M+H)^+$ = 888.

Step 2:

The Cbz-protected intermediate (176 mg, 0.1.98 mmol) in MeOH (25 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1.5 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. Trituration (dichloromethane/-ether) of the residue gave the product (50 mg, 41%). ESI-MS: $(M+H)^+$ = 620.

Example 121

3-Amino-N-[(2S,5S)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-N-piperidin-4-ylmethyl-propionamide



Step 1:

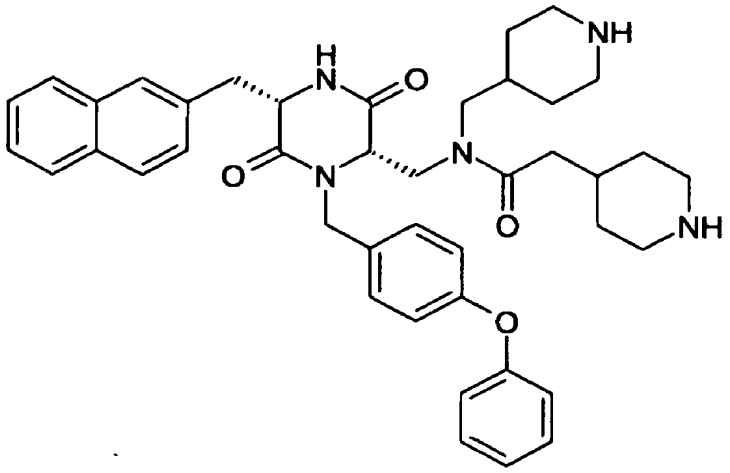
To the corresponding Cbz-protected product from general procedure G, step D (246 mg, 0.353 mmol), 3-N-Cbz-aminopropionic acid (236 mg, 1.06 mmol), HOBT (140 mg, 1.03 mmol), and TBTU (340 mg, 1.06 mmol) in THF (15 ml) is added at room temperature N-ethyl-diisopropylamine (0.2 ml, 1.14 mmol) and the mixture is stirred overnight. Sat. aq. sodium bicarbonate (40 ml) is added, the mixture stirred for 30 min., and then extracted with di-chloromethane (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloro-methane/MeOH 19:1) to give the bis-Cbz-protected intermediate (280 mg, 88%). ESI-MS: $(M+H)^+$ = 902.

Step 2:

The Cbz-protected intermediate (280 mg, 0.31 mmol) in MeOH (20 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 2 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo* to give the product (180 mg, 92%). ESI-MS: $(M+H)^+$ = 634.

Example 122

N-[(2S,5S)-5-Naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-2-piperidin-4-yl-N-piperidin-4-ylmethyl-acetamide



Step 1:

To the corresponding Cbz-protected product from general procedure G, step D (225 mg, 0.323 mmol), N-Boc-piperidin-4-yl-acetic acid (270 mg, 1.054 mmol), HOBT (140 mg, 1.03 mmol), and TBTU (340 mg, 1.06 mmol) in THF (20 ml) is added at room temperature N-ethyldiisopropylamine (0.2 ml, 1.14 mmol) and the mixture is stirred overnight. Sat. aq. sodium bicarbonate (40 ml) is added, the mixture stirred for 30 min., and then extracted with dichloromethane (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloromethane/MeOH 20:1) to give the bis-protected intermediate (162 mg, 54%). ESI-MS: $(M+HCOO)^-$ = 966.

Step 2:

To the bis-protected intermediate (162 mg, 0.176 mmol) in dichloromethane (5 ml) is added at room temperature TFA (0.36 ml) and the mixture is stirred for 2.5 h. Sat. aq. sodium bicarbonate is added, the mixture is stirred for 15 min., and then extracted with dichloromethane (3x70 ml). The combined org. layers are dried over sodium sulfate and concentrated *in vacuo* to give the crude Cbz-protected intermediate (135 mg, 93%). ESI-MS: $(M+H)^+$ = 822.

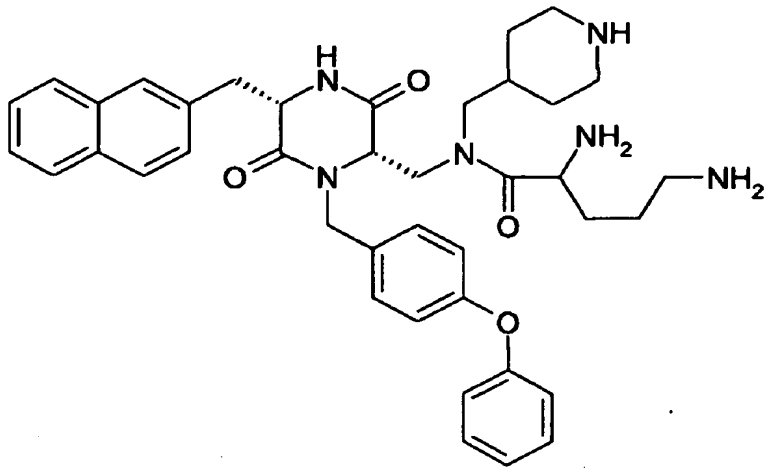
Step 3:

The crude Cbz-protected intermediate (135 mg, 0.164 mmol) in MeOH (25 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1.5 h. The catalyst is

removed by filtration and the filtrate is concentrated *in vacuo* to give the product (48 mg, 42%). ESI-MS: $(M+H)^+$ = 688.

Example 123

(RS)-2,5-Diamino-pentanoic acid [(2S,5S)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-piperidin-4-ylmethyl-amide



Step 1:

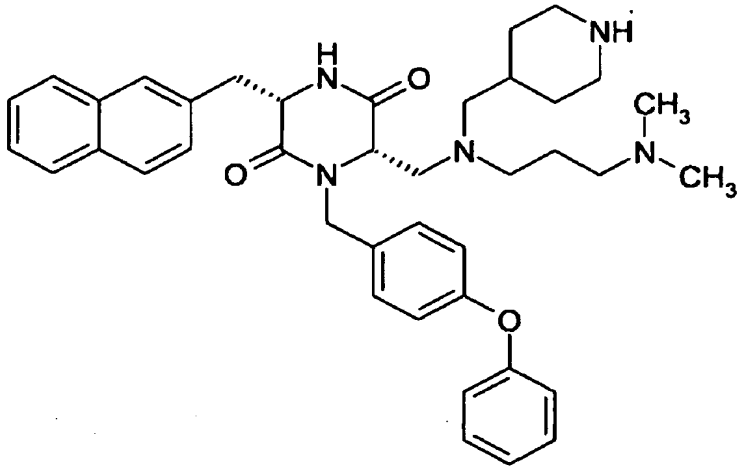
To the corresponding Cbz-protected product from general procedure G, step D (209 mg, 0.300 mmol), N,N'-di-Cbz-DL-ornithine (420 mg, 1.049 mmol), HOBT (140 mg, 1.03 mmol), and TBTU (340 mg, 1.06 mmol) in THF (15 ml) is added at room temperature N-ethyl-diisopropylamine (0.2 ml, 1.14 mmol) and the mixture is stirred for 20 h. Sat. aq. sodium bicarbonate (40 ml) is added, the mixture stirred for 30 min., and then extracted with ether (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloromethane/MeOH 20:1) to give the Cbz-protected intermediate (175 mg, 54%). ESI-MS: $(M+H)^+$ = 1078.

Step 2:

The Cbz-protected intermediate (160 mg, 0.148 mmol) in MeOH (25 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 110 min. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo* to give the product (75 mg, 75%). ESI-MS: $(M+H)^+$ = 677.

Example 124

(3S,6S)-6-{[(3-Dimethylamino-propyl)-piperidin-4-ylmethyl-amino]-methyl}-3-naphthalen-2-ylmethyl-1-(4-phenoxy-benzyl)-piperazine-2,5-dione



Step 1:

To the corresponding Cbz-protected product from general procedure G, step D (712 mg, 1.023 mmol) and 1,3-dibromopropane (0.5 ml, 4.904 mmol) in DMF (2.5 ml) is added at room temperature N-ethyldiisopropylamine (0.25 ml, 1.435 mmol) and the mixture is heated to 50°C for 6 h and then stirred at room temperature overnight. The mixture is diluted with water (50 ml) and extracted with ether (3x80 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue is purified by flash chromatography (silica, dichloromethane/MeOH 20:1) to give the intermediate bromide (495 mg, 59%). ESI-MS: $(M+H)^+$ = 818.

Step 2:

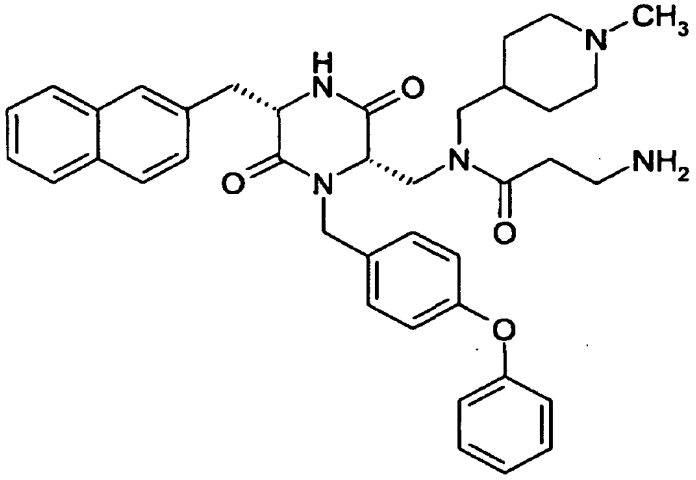
To the intermediate bromide (585 mg, 0.715 mmol) is added dimethylamine (2N in THF, 10 ml, 20 mmol) and the mixture is stirred at room temperature for 20 h. The formed precipitate is removed by filtration and the filtrate is concentrated *in vacuo*. Flash chromatography (alumina (activity II-III), dichloromethane/MeOH 40:1) afforded the Cbz-protected intermediate (432 mg, 77%). ESI-MS: $(M+H)^+$ = 783.

Step 3:

The Cbz-protected intermediate (432 mg, 0.552 mmol) in MeOH (30 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo* to give the product (333 mg, 93%). ESI-MS: $(M+H)^+$ = 648.

Example 125

3-Amino-N-(1-methyl-piperidin-4-ylmethyl)-N-[(2S,5S)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-propionamide



Step 1:

To the corresponding Cbz-protected product from general procedure G, step D (238 mg, 0.341 mmol), 3-N-Boc-propionic acid (200 mg, 1.06 mmol), HOBT (140 mg, 1.03 mmol), and TBTU (340 mg, 1.06 mmol) in THF (15 ml) is added at room temperature N-ethyldiiso-propylamine (0.2 ml, 1.14 mmol) and the mixture is stirred overnight. Sat. aq. sodium bicarbonate (40 ml) is added, the mixture stirred for 30 min., and then extracted with ether (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloromethane/MeOH 20:1) to give the bis -protected intermediate (252 mg, 85%). ESI-MS: $(M+H)^+$ = 902.

Step 2:

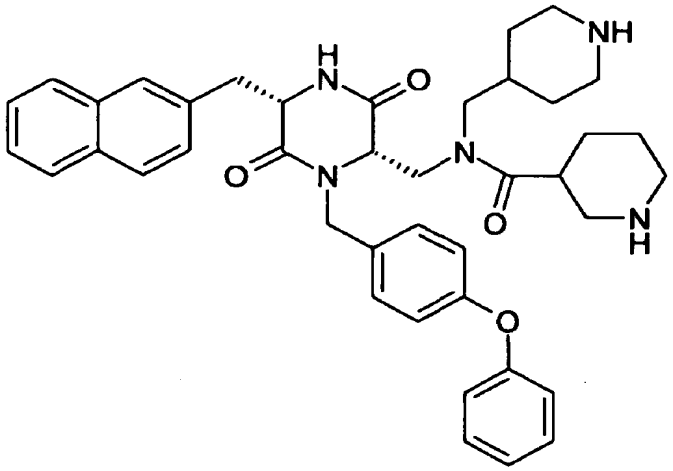
The bis-protected intermediate (243 mg, 0.28 mmol) in MeOH (25 ml) and formaldehyde (37% in water, 0.5 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo* Flash chromatography (alumina (activity II-III), dichloromethane/MeOH 30:1) gave the deprotected-alkylated intermediate (171 mg, 70%). ESI-MS: $(M+H)^+$ = 748.

Step 3:

To the Boc-protected intermediate (81 mg, 0.108 mmol) in dichloromethane (5 ml) is added at 0°C TFA (0.17 ml) and the mixture is stirred for 4 h. Sat. aq. sodium bicarbonate is added, the mixture is stirred for 15 min., and then extracted with dichloromethane (3x70 ml). The combined org. layers are dried over sodium sulfate and concentrated *in vacuo* Trituration (ether/petroleum ether) gave the product (30 mg, 42%). ESI-MS: $(M+H)^+$ = 648

Example 126

Piperidine-3-carboxylic acid [(2S,5S)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-piperidin-4-ylmethyl-amide



Step 1:

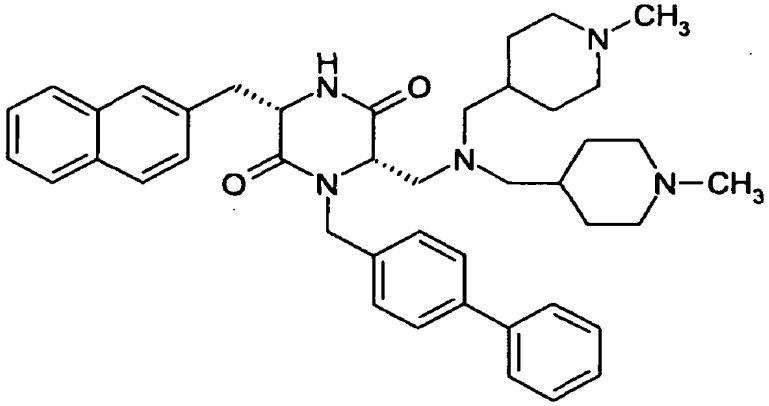
To the corresponding Cbz-protected product from general procedure G, step D (323 mg, 0.441 mmol), N-Cbz-piperidin-3-yl carboxylic acid (370 mg, 1.405 mmol), and TBTU (450 mg, 1.400 mmol) in THF (15 ml) is added at room temperature N-ethyldiisopropylamine (0.3 ml, 1.718 mmol) and the mixture is stirred at room temperature overnight and then heated to reflux for 8 h. Sat. aq. sodium bicarbonate (40 ml) is added, the mixture stirred for 15 min., and then extracted with ether (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloromethane/MeOH 20:1) to give a mixture of the 2 diastereoisomeric bis-Cbz-protected intermediates. Flash chromatography (silica, ethyl acetate/MeOH 100:0 → 50:1) afforded the 2 diastereoisomers (23% and 16%). ESI-MS: $(M+H)^+$ = 942.

Step 2:

The 2 Cbz-protected diastereoisomers are submitted separately to hydrogenation in MeOH (20 ml) at 50 psi in the presence of Pd/C (10%) at 50°C for 2 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo* to give the product (41% and 35%). ESI-MS: $(M+H)^+$ = 674.

Example 127

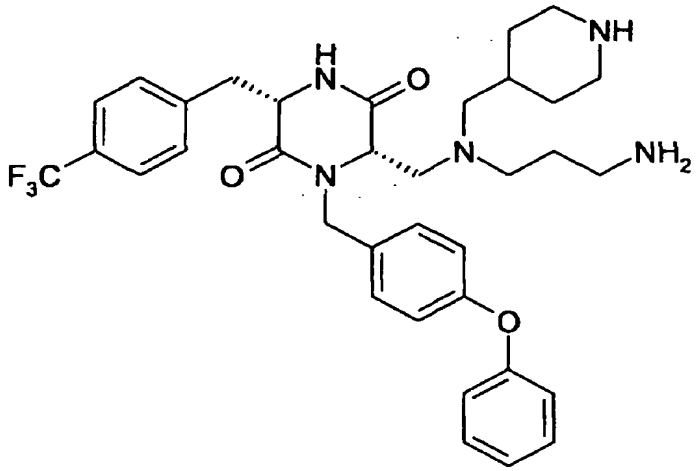
(3S,6S)-1-Biphenyl-4-ylmethyl-6-{[bis-(1-methyl-piperidin-4-ylmethyl)-amino]-methyl}-3-naphthalen-2-ylmethyl-piperazine-2,5-dione



To the corresponding product of general procedure G, step G (171 mg, 0.266 mmol) and formaldehyde (37% in water, 0.1 ml, 1.232 mmol) in THF (10 ml) is added at room temperature sodium triacetoxyborohydride (200 mg, 0.944 mmol) and the mixture is stirred for 3 days. Sat. aq. sodium bicarbonate is added, the mixture is stirred for 15 min., and then extracted with ethyl acetate (3x80 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue is purified by flash chromatography (alumina (activity II-III), dichloromethane/MeOH 30:1 → 20:1) to give the product (54 mg, 30%). ESI-MS: $(M+H)^+$ = 672.

Example 128

(3S,6S)-6-{[(3-Amino-propyl)-piperidin-4-ylmethyl-amino]-methyl}-1-(4-phenoxy-benzyl)-3-(4-trifluoromethyl-benzyl)-piperazine-2,5-dione



Step 1:

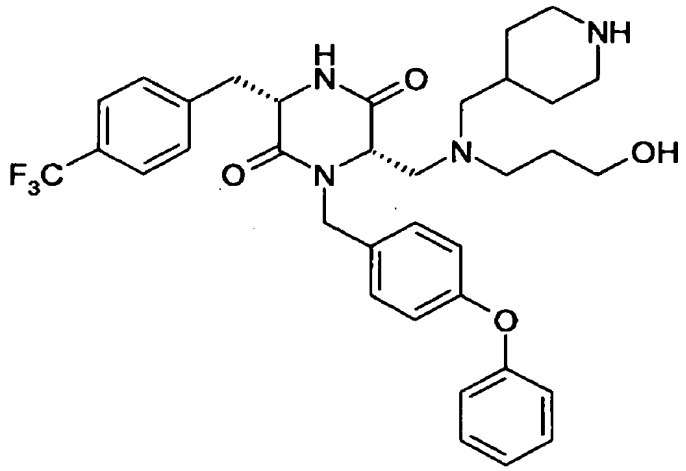
To the corresponding Cbz-protected product from general procedure G, step D (543 mg, 0.760 mmol) and 3-N-Cbz-propionaldehyde (480 mg, 2.320 mmol) in THF (35 ml) is added p-toluenesulfonic acid hydrate (144 mg, 0.760 mmol) and the mixture is stirred for 1 h. Sodium triacetoxyborohydride (600 mg, 2.690 mmol) is added and the mixture is stirred 6 h. Sat. aq. sodium bicarbonate is added, the mixture stirred for 30 min., and then extracted with ethyl acetate (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloro-methane/MeOH 33:1) to give the bis-Cbz-protected intermediate (690 mg, quant. yield). ESI-MS: $(M+H)^+$ = 906.

Step 2:

The bis-Cbz-protected intermediate (690 mg, 0.760 mmol) in MeOH (30 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 4 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The residue purified by HPLC (ZorbaxSB-C18 (5 µm) column, gradient of water/MeCN + 0.1% formic acid, detection at 254 nm and 230 nm) to give the product (470 mg, 97%). ESI-MS: $(M+H)^+$ = 638.

Example 129

(3S,6S)-6-{[(3-Hydroxy-propyl)-piperidin-4-ylmethyl-amino]-methyl}-1-(4-phenoxy-benzyl)-3-(4-trifluoromethyl-benzyl)-piperazine-2,5-dione



Step 1:

To the corresponding Cbz-protected product from general procedure G, step D (225 mg, 0.315 mmol) and 3-bromo-propanol (0.1 ml, 1.073 mmol) in DMF (2 ml) is added at room temperature N-ethyldiisopropylamine (0.2 ml, 1.148 mmol) and the mixture is heated to

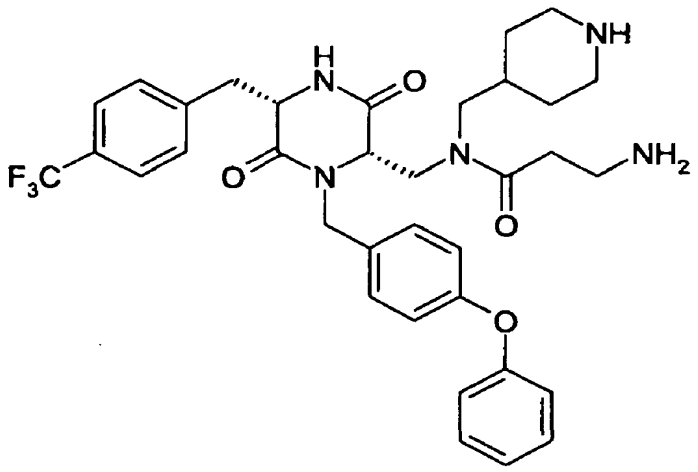
120°C for 3 h. 3-bromo-propanol (0.1 ml, 1.073 mmol) is added and the mixture heated to 120°C for another 3 h. Water (50 ml) is added and the aq. layer is extracted with ether (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue is purified by flash chromatography (alumina (activity II-III), dichloromethane/MeOH 30:1 → 20:1) to give the Cbz-protected intermediate (70 mg, 29%). ESI-MS: $(M+H)^+$ = 773.

Step 2:

The Cbz-protected intermediate (70 mg, 0.091 mmol) in MeOH (25 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1.5 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. The triturated (dichloromethane/ether) to give the product (29 mg, 50%). ESI-MS: $(M+H)^+$ = 639.

Example 130

3-Amino-N-[(2S,5S)-3,6-dioxo-1-(4-phenoxy-benzyl)-5-(4-trifluoromethyl-benzyl)-piperazin-2-ylmethyl]-N-piperidin-4-ylmethyl-propionamide



Step 1:

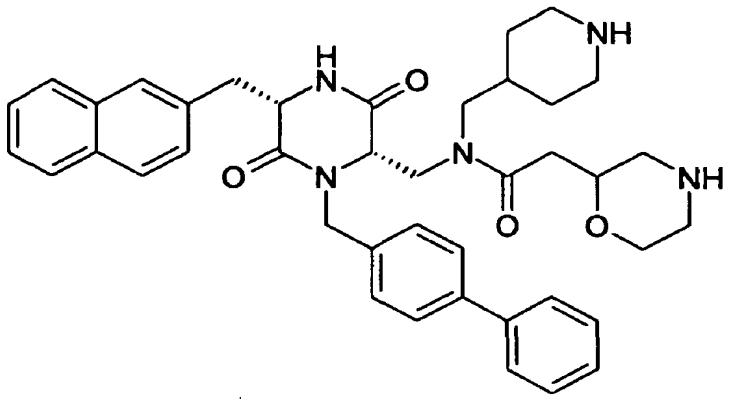
To the corresponding Cbz-protected product from general procedure G, step D (460 mg, 0.644 mmol), 3-N-Cbz-aminopropionic acid (425 mg, 1.904 mmol), HOBT (283 mg, 1.841 mmol), and TBTU (614 mg, 1.891 mmol) in THF (30 ml) is added at room temperature N-ethyldiisopropylamine (0.47 ml, 2.689 mmol) and the mixture is stirred for 4 days. Sat. aq. sodium bicarbonate (40 ml) is added, the mixture stirred for 30 min., and then extracted with dichloromethane (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloromethane/MeOH 49:1 → 19:1) to give the bis-Cbz-protected intermediate (400 mg, 67%). ESI-MS: $(M+H)^+$ = 920.

Step 2:

The Cbz-protected intermediate (266 mg, 0.0.289 mmol) in MeOH (40 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 75 min. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. Trituration (dichloromethane/-ether) of the residue gave the product (120 mg, 64%). ESI-MS: $(M+H)^+$ = 652.

Example 131

N-((2S,5S)-1-Biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-2-(RS)-morpholin-2-yl-N-piperidin-4-ylmethyl-acetamide



Step 1:

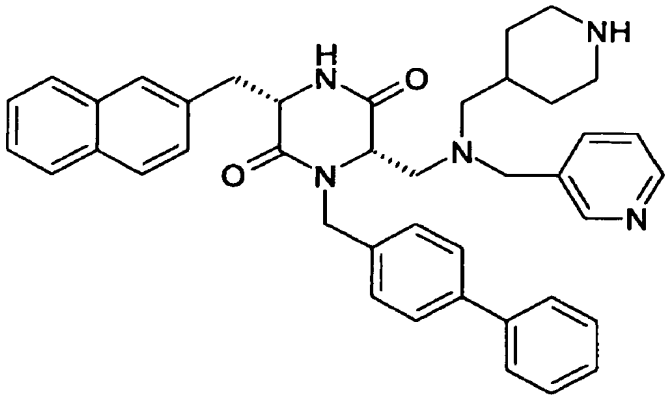
To the corresponding Cbz-protected product from general procedure G, step D (237 mg, 0.349 mmol), N-Cbz-2carboxymorpholine (300 mg, 1.074 mmol), HOBT (130 mg, 0.960 mmol), and TBTU (320 mg, 0.997 mmol) in THF (15 ml) is added at room temperature N-ethyldiisopropylamine (0.2 ml, 1.139 mmol) and the mixture is stirred for 20 h. Sat. aq. sodium bicarbonate (40 ml) is added, the mixture stirred for 30 min., and then extracted with ether (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloromethane/MeOH 30:1 → 20:1) to give the bis-Cbz-protected intermediate (198 mg, 60%). ESI-MS: $(M+H)^+$ = 942.

Step 2:

The Cbz-protected intermediate (189 mg, 0.201 mmol) in MeOH (30 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1.5 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. Trituration (dichloromethane/-ether) of the residue gave the product (126 mg, 93%). ESI-MS: $(M+H)^+$ = 674.

Example 132

(3S,6S)-1-Biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-6-[(piperidin-4-ylmethyl-pyridin-3-ylmethyl-amino)-methyl]-piperazine-2,5-dione



Step 1:

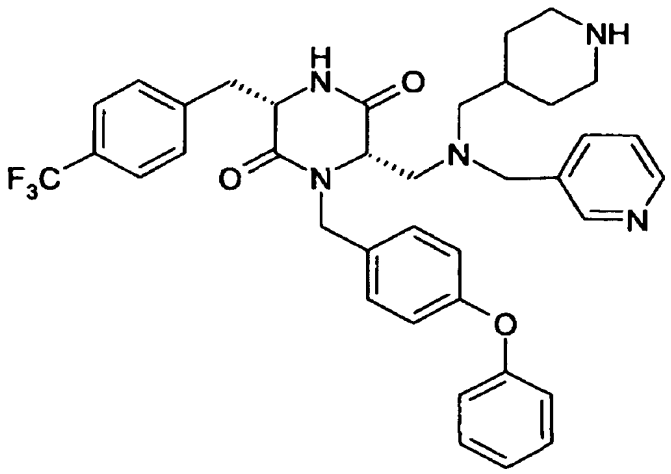
To the corresponding Cbz-protected product from general procedure G, step D (238 mg, 0.35 mmol) and 3-pyridylcarbaldehyde (120 mg, 1.12 mmol) in THF (15 ml) is added sodium triacetoxyborohydride (250 mg, 1.121 mmol) is added and the mixture is stirred for 20 h. Sat. aq. sodium bicarbonate is added, the mixture stirred for 30 min., and then extracted with ethyl acetate (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloromethane/MeOH 20:1 → 15:1) to give the Cbz-protected intermediate (257 mg, 95%). ESI-MS: $(M+H)^+$ = 772.

Step 2:

The Cbz-protected intermediate (260 mg, 0.32 mmol) in MeOH (30 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 2 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo* to give the product (180 mg, 75%). ESI-MS: $(M+H)^+$ = 638.

Example 133

(3S,6S)-1-(4-Phenoxy-benzyl)-6-[(piperidin-4-ylmethyl-pyridin-3-ylmethyl-amino)-methyl]-3-(4-trifluoromethyl-benzyl)-piperazine-2,5-dione



Step 1:

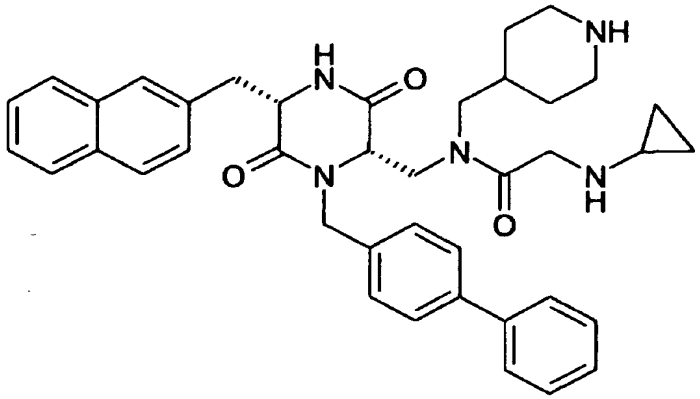
To the corresponding Cbz-protected product from general procedure G, step D (250 mg, 0.25 mmol) and 3-pyridylcarbaldehyde (120 mg, 1.12 mmol) in THF (15 ml) is added sodium triacetoxyborohydride (250 mg, 1.12 mmol) is added and the mixture is stirred overnight. Sat. aq. sodium bicarbonate is added, the mixture stirred for 30 min., and then extracted with ethyl acetate (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloromethane/MeOH 30:1) to give the Cbz-protected intermediate (230 mg, 81%). ESI-MS: $(M+H)^+ = 806$.

Step 2:

The Cbz-protected intermediate (220 mg, 0.273 mmol) in MeOH (50 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. Trituration (dichloromethane/-ether) gave the product (173 mg, 94%). ESI-MS: $(M+H)^+ = 672$.

Example 134

N-((2S,5S)-1-Biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-2-cyclopropylamino-N-piperidin-4-ylmethyl-acetamide



Step 1:

To the corresponding Cbz-protected product from general procedure G, step D (570 mg, 0.837 mmol) and bromoacetyl bromide (0.075 ml, 0.862 mmol) in dichloromethane (20 ml) is added at 0°C N-ethyldiisopropylamine (0.2 ml, 1.148 mmol) and the mixture is stirred at 0°C for 30 min. Sat. aq. sodium bicarbonate is added, the mixture is stirred for 15 min., and then extracted with dichloromethane (3x80 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue is purified by trituration (dichloromethane/ether) to afford the intermediate bromide (580 mg, 86%). ESI-MS: $(M+H)^+$ = 801.

Step 2:

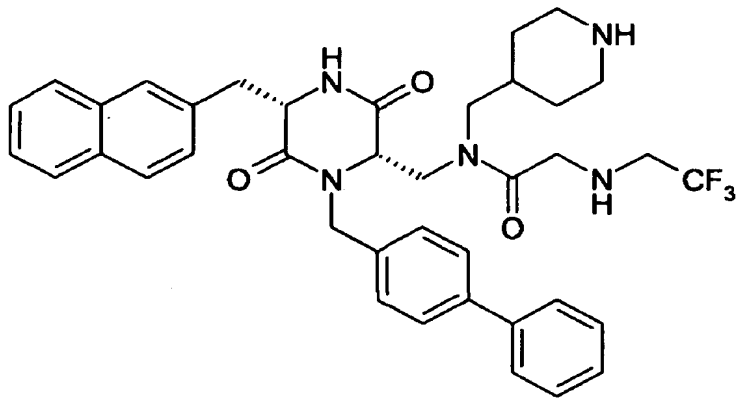
The intermediate bromide (285 mg, 0.355 mmol) and cyclopropylamine (150 mg, 2.627 mmol) in THF (5 ml) is stirred at room temperature for 3 days. The mixture is concentrated *in vacuo* and the residue purified by flash chromatography (alumina (activity II-III), dichloromethane/MeOH 40:1 → 20:1) to give the Cbz-protected intermediate (260 mg, 94%). ESI-MS: $(M+H)^+$ = 778.

Step 3:

The Cbz-protected intermediate (250 mg, 0.321 mmol) in MeOH (30 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 2 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo* to give the product (1350 mg, 65%). ESI-MS: $(M+H)^+$ = 644.

Example 135

N-((2S,5S)-1-Biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-2-(2,2,2-trifluoro-ethylamino)-acetamide



Step 1:

To the corresponding Cbz-protected product from general procedure G, step D (570 mg, 0.837 mmol) and bromoacetyl bromide (0.075 ml, 0.862 mmol) in dichloromethane (20 ml) is added at 0°C N-ethyldiisopropylamine (0.2 ml, 1.148 mmol) and the mixture is stirred at 0°C for 30 min. Sat. aq. sodium bicarbonate is added, the mixture is stirred for 15 min., and then extracted with dichloromethane (3x80 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue is purified by trituration (dichloromethane/ether) to afford the intermediate bromide (580 mg, 86%). ESI-MS: $(M+H)^+$ = 801.

Step 2:

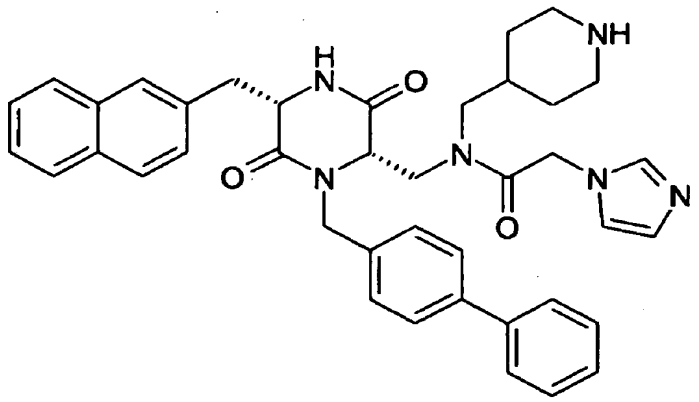
The intermediate bromide (285 mg, 0.355 mmol) and 2,2,2-trifluoroethylamine (300 mg, 3.028 mmol) in THF (5 ml) is stirred at room temperature for 3 days. The mixture is concentrated *in vacuo* and the residue purified by flash chromatography (silica, dichloromethane/MeOH 20:1 → 15:1) to give the Cbz-protected intermediate (290 mg, 99%). ESI-MS: $(M+H)^+$ = 820.

Step 3:

The Cbz-protected intermediate (280 mg, 0.341 mmol) in MeOH (30 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 2 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo* to give the product (1710 mg, 73%). ESI-MS: $(M+H)^+$ = 686.

Example 136

N-((2S,5S)-1-Biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-2-imidazol-1-yl-N-piperidin-4-ylmethyl-acetamide



Step 1:

To the corresponding Cbz-protected product from general procedure G, step D (570 mg, 0.837 mmol) and bromoacetyl bromide (0.075 ml, 0.862 mmol) in dichloromethane (20 ml) is added at 0°C N-ethyldiisopropylamine (0.2 ml, 1.148 mmol) and the mixture is stirred at 0°C for 30 min. Sat. aq. sodium bicarbonate is added, the mixture is stirred for 15 min., and then extracted with dichloromethane (3x80 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue is purified by trituration (dichloromethane/ether) to afford the intermediate bromide (580 mg, 86%). ESI-MS: $(M+H)^+$ = 801.

Step 2:

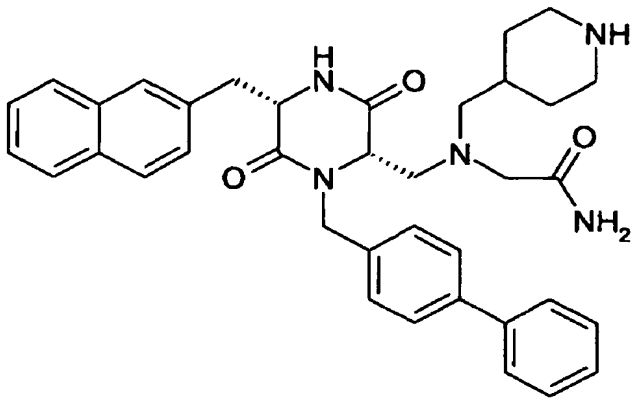
The intermediate bromide (306 mg, 0.382 mmol) and imidazole (100 mg, 1.469 mmol) in THF (10 ml) is heated to reflux for 3 h. Water (50 ml) is added and the aq. layer is extracted with ethyl acetate (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (alumina (activity II-III), dichloromethane/MeOH 30:1 → 20:1) to give the Cbz-protected intermediate (180 mg, 60%). ESI-MS: $(M+H)^+$ = 789.

Step 3:

The Cbz-protected intermediate (181 mg, 0.217 mmol) in MeOH (30 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1 h. The catalyst is removed by filtration, the filtrate is concentrated *in vacuo*, and the residue is triturated (dichloromethane/ether) to give the product (123 mg, 87%). ESI-MS: $(M+H)^+$ = 655.

Example 137

2-[((2S,5S)-1-Biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-piperidin-4-ylmethyl-amino]-acetamide



Step 1:

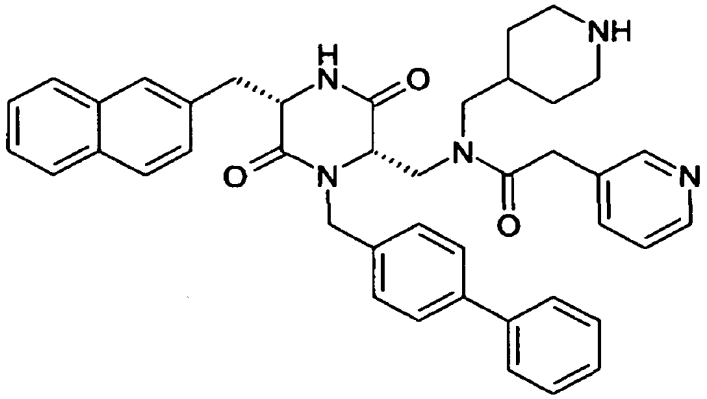
To the corresponding Cbz-protected product of general procedure G, step D (680 mg, 1.0 mmol) and 2-bromoactamid (155 mg, 1.1 mmol) in DMF (10 ml) is added sodium bicarbonate (233 mg, 2.2 mmol) and the mixture is stirred at 80°C for 5 h. The reaction mixture is poured into ice water (200 ml), the white precipitate is collected by filtration and washed with water to give the intermediate (730 mg, 99%). ESI-MS: $(M+H)^+$ = 738.

Step 2:

The Cbz-protected intermediate (730 mg, 0.989 mmol) in MeOH (50 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 25 min. The catalyst is removed by filtration. The filtrate is concentrated *in vacuo* and washed with ether to give the product (400 mg, 67%). ESI-MS: $(M+H)^+$ = 604.

Example 138

N-((2S,5S)-1-Biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-2-pyridin-3-yl-acetamide



Step 1:

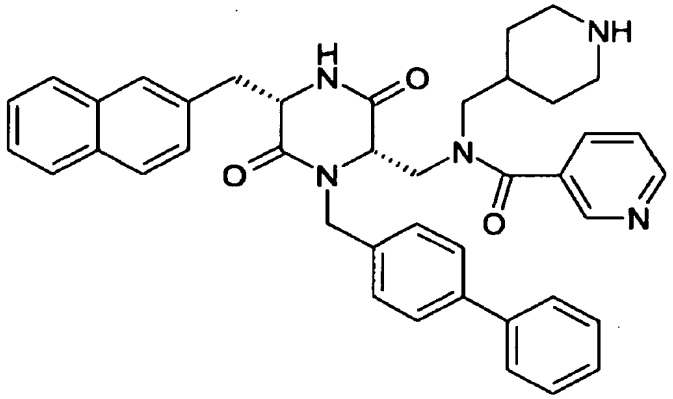
To the corresponding Cbz-protected product from general procedure G, step D (238 mg, 0.349 mmol), 3-pyridylacetic acid (150 mg, 1.094 mmol), HOBT (130 mg, 0.960 mmol), and TBTU (320 mg, 0.997 mmol) in THF (15 ml) is added at room temperature N-ethyldiisopropylamine (0.25 ml, 1.424 mmol) and the mixture is heated to reflux for 5 h. Sat. aq. sodium bicarbonate (40 ml) is added, the mixture stirred for 10 min., and then extracted with ethyl acetate (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloromethane/MeOH 20:1 → 10:1) to give the Cbz-protected intermediate (257 mg, 92%). ESI-MS: $(M+H)^+$ = 800.

Step 2:

The Cbz-protected intermediate (247 mg, 0.309 mmol) in MeOH (30 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1.5 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. Trituration (dichloromethane/-ether) of the residue gave the product (158 mg, 77%). ESI-MS: $(M+H)^+$ = 666.

Example 139

N-((2S,5S)-1-Biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-nicotinamide



Step 1:

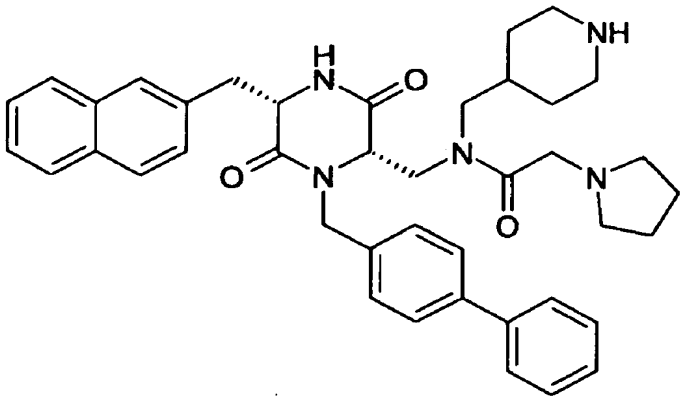
To the corresponding Cbz-protected product from general procedure G, step D (238 mg, 0.349 mmol) and nicotinic acid chloride (100 mg, 0.545 mmol) in dichloromethane (10 ml) is added at 0°C N-ethyldiisopropylamine (0.25 ml, 1.424 mmol) and the mixture is stirred at 0°C for 1 h. Sat. aq. sodium bicarbonate (40 ml) is added, the mixture stirred for 10 min., and then extracted with dichloromethane (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (silica, dichloromethane/MeOH 20:1 → 15:1) to give the Cbz-protected intermediate (257 mg, 93%). ESI-MS: $(M+H)^+$ = 786.

Step 2:

The Cbz-protected intermediate (247 mg, 0.314 mmol) in MeOH (30 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1.5 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. Trituration (dichloromethane/-ether) of the residue gave the product (150 mg, 73%). ESI-MS: $(M+H)^+$ = 652.

Example 140

N-((2S,5S)-1-Biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-2-pyrrolidin-1-yl-acetamide



Step 1:

To the corresponding Cbz-protected product from general procedure G, step D (570 mg, 0.837 mmol) and bromoacetyl bromide (0.075 ml, 0.862 mmol) in dichloromethane (20 ml) is added at 0°C N-ethyldiisopropylamine (0.2 ml, 1.148 mmol) and the mixture is stirred at 0°C for 30 min. Sat. aq. sodium bicarbonate is added, the mixture is stirred for 15 min., and then extracted with dichloromethane (3x80 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue is purified by trituration (dichloromethane/ether) to afford the intermediate bromide (580 mg, 86%). ESI-MS: $(M+H)^+$ = 801.

Step 2:

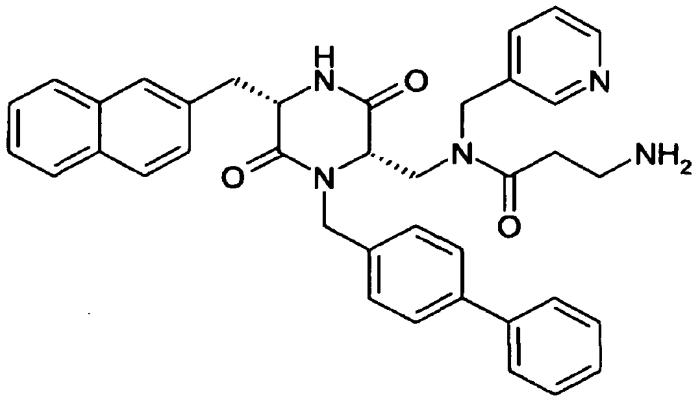
The intermediate bromide (323 mg, 0.382 mmol) and pyrrolidine (100 mg, 1.406 mmol) in THF (10 ml) is stirred at room temperature for 1 h. Sat. aq. sodium bicarbonate is added and the aq. layer is extracted with ethyl acetate (3x80 ml). The combined org. layers are dried over sodium sulfate and the residue is purified by flash chromatography (alumina (activity II-III), dichloromethane/MeOH 10:1) to give the Cbz-protected intermediate (200 mg, 66%). ESI-MS: $(M+H)^+$ = 792.

Step 3:

The Cbz-protected intermediate (190 mg, 0.240 mmol) in MeOH (30 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo* to give the product (160 mg, quant.). ESI-MS: $(M+H)^+$ = 658.

Example 141

3-Amino-N-((2S,5S)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-pyridin-3-ylmethyl-propionamide



Step 1:

The corresponding product of general procedure E, step E (1.0 g, 2.224 mmol), 3-pyridylcarbaldehyde (300 mg, 2.801 mmol), and a trace of p-toluenesulfonic acid is heated to reflux for 2 h. The precipitate is collected by filtration and dried under high vacuum (1.080 g, 90%).

Step 2:

The Schiff's base (270 mg, 0.501 mmol) in MeOH (30 ml) is hydrogenated (50 psi) in the presence of Raney nickel (130 mg) at 50°C for 2 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. Trituration (dichloromethane/ether) afforded the intermediate (216 mg, 80%). ESI-MS: $(M+H)^+$ = 541.

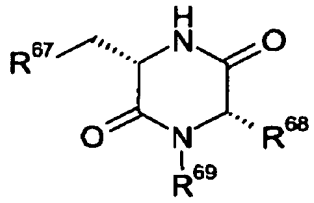
Step 3:

To the intermediate from the previous step (220 mg, 0.407 mmol), 3-N-Cbz-propionic acid (280 mg, 1.254 mmol), HOBT (160 mg, 1.182 mmol), and TBTU (370 mg, 1.152 mmol) in THF (15 ml) is added at room temperature N-ethyldiisopropylamine (0.3 ml, 1.709 mmol) and the mixture is stirred for 1 day. Sat. aq. sodium bicarbonate (40 ml) is added, the mixture stirred for 10 min., and then extracted with ether (3x70 ml). The combined org. layers are dried over sodium sulfate, concentrated *in vacuo*, and the residue purified by flash chromatography (alumina (activity II-III), dichloromethane/MeOH 30:1) to give the Cbz-protected intermediate (115 mg, 38%). ESI-MS: $(M+H)^+$ = 746.

Step 4: The Cbz-protected intermediate (110 mg, 0.140 mmol) in MeOH (30 ml) is hydrogenated (50 psi) in the presence of Pd/C (10%) at 50°C for 1.5 h. The catalyst is removed by filtration and the filtrate is concentrated *in vacuo*. Trituration (dichloromethane/-ether) of the residue gave the product (75 mg, 88%). ESI-MS: $(M+H)^+$ = 612.

Examples 142 to 148

Active compounds prepared according to the general procedure C of general formula (Ig) are shown in Table IX:



Formula (Ig)

Table IX

Example No	R^{67}	R^{68}	R^{69}	ESI-MS
142	2-naphthyl	4-amino-butyl	biphenyl-4-ylmethyl	$(M+H)^+$ = 492
143	2-naphthyl	4-amino-butyl	4-phenoxy-benzyl	$(M+H)^+$ = 508
144	3,4-Cl_2-C_6H_3	4-amino-butyl	4-phenoxy-benzyl	$(M+H)^+$ = 526
145	2-naphthyl	4-amino-butyl	9H-fluoren-2-ylmethyl	$(M+H)^+$ = 504
146	1-naphthyl	4-amino-butyl	4-phenoxy-benzyl	$(M+H)^+$ = 508
147	1-naphthyl	4-amino-butyl	9H-fluoren-2-ylmethyl	$(M+H)^+$ = 504
148	1-naphthyl	4-amino-butyl	4-benzyloxy-benzyl	$(M+H)^+$ = 522

BIOLOGICAL METHODS

Melanocortin receptor 1 (MC1) binding assay

The MC1 receptor binding assay is performed on HEK293 cell membranes stably expressing the MC1 receptor. The assay is performed in a total volume of 250 µl; 25 µl ^{125}NDP-α-MSH (≈ 33 pM in final concentration) 25 µl test compound/control and 200 µl cell membrane (35 µg/ml). The samples are incubated at 30°C for 90 min in the Greiner microtitter plates and separated on GF/B filters that are pre-wetted for 60 min in 0.5% PEI, and washed 2-3 times with NaCl (0.9%) before separation of bound from unbound radio ligand by filtration. After filtration the filters are washed with ice-cold 0.9% NaCl 10 times. The filters are dried at 50°C for 30 min, sealed and 30 µl Microscint 0 (Packard, cat no. 6013616) are added to each well and the plates are counted in a Topcounter 1 min/well.

The data are analysed by a non-linear regression analysis of binding curves, using a windows program GraphPad Prism, GraphPad software, USA.

Melanocortin receptor 1, 3 and 5 (MC1, MC3 and MC5) cAMP functional assay

The cAMP assays for MC1, MC3 and MC5 receptors are performed on cells stably expressing the MC1, MC3 and MC5 receptors respectively. The receptors were cloned from cDNA by PCR and inserted into the pcDNA 3 expression vector. Stable clones were selected using 1 mg /ml G418.

Cells at app. 80-90% confluence are washed 3x with PBS, lifted from the plates with Versene and diluted in PBS. Centrifuged 2 min at 1300 rpm, and the supernatant removed. The cells are washed twice with stimulation buffer, and resuspended in stimulation buffer to a final concentration of $1x10^6$ cells/ml. (Use 7 ml/96 well plate). 50 µl cell suspension is added to the FlashPlate containing 50 µl of test-compound or reference compound (all diluted in H_2O). The plates are incubated for 30 minutes at room temperature (RT) on a plate-shaker that shakes at low rate. The reaction is stopped with 100 µl Detection Mixpro well (Detection Mix= 11 ml Detection Buffer + 100 µl (~2µCi) cAMP [^{125}I] Tracer). The plates are then sealed with plastic, shaken for 30 minutes, and allowed to stand overnight (or for 2 hours), and counted in the Topcounter 1 min/well. In general the assay procedure described in the kit-protocol (Flash Plate® cAMP assay (NEN™ Life Science Products cat no SMP004)) is followed, however the cAMP standards are diluted in H_2O and <u>not</u> in stimulation buffer.

Melanocortin receptor 4 (MC4) binding assay

In vitro ^{125}NDP-α-MSH binding to recombinant SF9 cells expressing human MC4 receptor (filtration assay).

The assay is performed in 5 ml minisorb vials, (Sarstedt No. 55.526) or in 96 well filterplate, Millipore MADVN 6550 and using SF9 cells expressing the human MC4 receptor (obtained from Professer Wikberg, Uppsala, Sweden). The SF9 cells are kept at -80°C until assay, and the assays is run directly on a dilution of this cell suspension, without further preparation. The suspension is diluted to give maximal 10% specific binding, app 50-100 fold dilution. The assay is performed in a total volume of 200 µl; 50 µl cell suspension, 50 µl ^{125}NDP-α-MSH (≈ 79 pM in final concentration), 50 µl test-peptide and 50 µl binding buffer pH 7 is mixed and incubated for 2 h at 25°C. (Binding buffer; 25 mM HEPES pH 7.0, 1 mM $CaCl_2$, 1 mM $MgSO_4$, 1 mM EGTA, 0.02% Bacitracin and 0.2% BSA). Peptides are dissolved in H_2O and diluted in binding buffer. Radioligand and membranes are diluted in binding buffer. The incubation is stopped by dilution with 5 ml ice-cold 0.9% NaCl, followed by rapid filtration through Whatman GF/C filters pre-treated for 1 hour with 0.5% polyethyleneimine. The filters are washed with 3x5 ml ice-cold NaCl. The radioactivity retained on the filters is counted using a Cobra II auto gamma counter.

The data are analysed by a non-linear regression analysis of binding curves, using a windows program GraphPad Prism, GraphPad software, USA.

Melanocortin receptor 4 (MC4) cAMP assay

BHK cells expressing the MC4 receptor are stimulated with potential MC4 agonists, and the degree of stimulation of cAMP is measured using the Flash Plate® cAMP assay (NEN™ Life Science Products cat no SMP004).

The MC4 receptor expressing BHK cells were made by transfecting the cDNA encoding MC4 receptor into BHK570/KZ10-20-48, and selecting for stable clones expressing the MC4 receptor. The MC4 receptor cDNA is bought from Euroscreen in addition to a CHO cell line expressing the MC4 receptor. The cells are grown in DMEM, 10% FCS, 1 mg/ml G418, 250 nM MTXand 1% penicillin/streptomycin.

Cells at app. 80-90% confluence are washed 3xwith PBS, lifted from the plates with Versene and diluted in PBS. Centrifuged 2 min at 1300 rpm, and the supernatant removed. The cells are washed twice with stimulation buffer, and resuspended in stimulation buffer to a final concentration of $0.75x10^6$ cells/ml. (Use 7 ml/96 well plate). 50 µl cell suspension is added to the Flashplate containing 50 µl of test-compound or reference compound (all diluted in H_2O). The mixture is shaken for 5 minutes, and allowed to stand for 25 minutes at RT. The reaction is stopped with 100 µl Detection Mixpro well (Detection Mix= 11 ml Detection Buffer

+ 100 µl (~2µCi) cAMP [^{125}I] Tracer). The plates are then sealed with plastic, shaken for 30 minutes, and allowed to stand overnight (or for 2 hours), and counted in the Topcounter 2 min/well. In general the assay procedure described in the kit-protocol (Flash Plate® cAMP assay (NEN™ Life Science Products cat no SMP004)) is followed, however the cAMP standards are diluted in H_2O and not in stimulation buffer.

EC_{50} values is calculated by non-linear regression analysis of dose response curves (6 points minimum) using the windows program GraphPad Prism, GraphPad software, USA. All results are expressed in nM.

PHARMACOLOGICAL METHODS

Assay (I) Experimental protocol for efficacy testing on appetite with MC4 analogues, using a schedule-fed rat model.

TAC:SPRD @mol rats or Wistar rats from M&B Breeding and Research Centre A/S, Denmark are used for the experiments. The rats have a bodyweight 200-250 g at the start of experiment. The rats arrive at least 10-14 days before start of experiment with a bodyweight of 180-200 g. Each dose of compound is tested in a group of 8 rats. A vehicle group of 8 rats is included in each set of testing.

When the animals arrive they are housed individually. After a habituating period of 4-7 days with free access to food and water, the schedule feeding is initiated. The rats are allowed to eat from 08 am to 01 pm each day. In the remaining period only access to water is allowed. They are kept on this feeding schedule for 8 days before start of experiment. In this period the animals are handled and dosed in the relevant way (ip, po, sc.) with saline at least 3 times. The experiment is conducted in the rat home cages. Immediately before dosing the rats are randomised to the different treatment groups (n=8) by bodyweight. They are dosed according to bodyweight at 08 am, with a 1 ml/kg solution either, ip, po or sc. The dosing time is recorded for each group. Following dosing the rats are returned to their home cages, where they now have access to food and water. The food consumption is recorded individually, each hour for 3 hours. At the end of the experimental session, the animals are euthanised.

The individual data are recorded in Microsoft excel sheets. Outliers are excluded after using the Grubbs statistical evaluation test for outliers and the result presented graphically by using the GraphPad Prism program.

Drug:
Vehicle 1 ml/kg i.p

Diet Consumed, Grams

	Raw Data					Diet Consumed			Weight of RAT, g
Rat #	Diet in	Time in	1 hr	2 hr	3hr	1hr	2hr	3 hr	
33	150.7	8.13	148.7	144.3	143.6	2	6.4	7.1	232.4
29	150.4		147.4	143.0	140.3	3.0	7.4	10.1	226.8
15	143.7		140.7	136.9	133.3	3.0	6.8	10.4	198.7
20	126.7		124.7	121.4	117.4	2.0	5.3	9.3	234.1
11	113.5		111.2	105.6	101.3	2.3	7.9	12.2	215
13	99.1		95.5	91.5	89.4	3.6	7.6	9.7	235.3
2	116.7		115.3	111.2	108.9	1.4	5.5	7.8	202.2
40	147.0		144.0	138.8	137.1	3.0	8.2	9.9	207.1
X						2.5	6.9	9.6	219.0
sd						.7	1.1	1.6	15.1

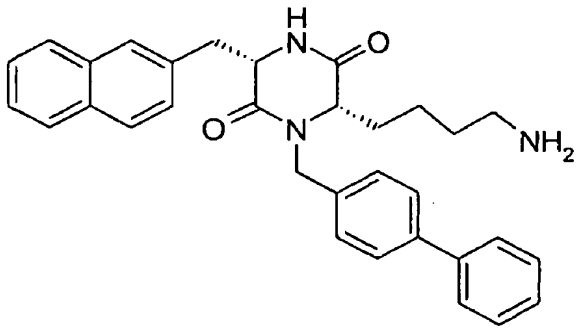
5

Drug:
Sibutramine, 3 mg/kg i.p.

Diet Consumed. Grams

	Raw Data					Diet Consumed			Weight of RAT, g
Rat #	Diet in	Time in	1 hr	2 hr	3hr	1hr	2hr	3 hr	
17	131.2	8.27	128.8	125.6	123	2.4	5.6	8.2	218.2
4	122.0		121.1	118.0	116.0	0.9	4.0	6.0	238.3
14	146.8		142.7	139.4	137.9	4.1	7.4	8.9	186
7	144.1		141.5	137.2	134.6	2.6	6.9	9.5	222
22	134.9		130.8	127.2	123.7	4.1	7.7	11.2	233.9
30	121.2		119.3	114.2	112.2	1.9	7.0	9.0	202.8
35	128.6		123.7	121.4	118.6	4.9	7.2	10.0	211.5
31	147.4		140.1	136.9	135.1	7.3	10.5	12.3	217.1
X						3.5	7.0	9.4	216.2
sd						2.0	1.8	1.9	16.7

Drug:
(S,S)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-piperazine-2,5-dione (example 23) 1 mg/kg i.p.



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Diet Consumed, Grams

	Raw Data					Diet Consumed			Weight of RAT, g
Rat #	Diet in	Time in	1 hr	2 hr	3hr	1hr	2hr	3 hr	
10	117.7	8.40	113.4	110.1	108	4.3	7.6	9.7	253.5
16	140.7		139.3	136.2	133.7	1.4	4.5	7.0	203.6
32	137.0		135.0	132.3	128.6	2.0	4.7	8.4	211.2
28	162.4		160.3	153.4	153.4	2.1	9.0	9.0	228.3
21	140.0		138.4	134.2	134.2	1.6	5.8	5.8	228.6
9	129.0		127.6	123.4	120.9	1.4	5.6	8.1	239.8
5	152.8		149.4	146.4	142.2	3.4	6.4	10.6	204.8
38	140.3		137.5	133.5	131.6	2.8	6.8	8.7	217.5
X						2.4	6.3	8.4	223.4
sd						1.0	1.5	1.5	17.5

Drug:
(S,S)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-piperazine-2,5-dione (example 23) 3 mg/kg i.p.

Diet Consumed, Grams

	Raw Data					Diet Consumed			Weight of RAT, g
Rat #	Diet in	Time in	1 hr	2 hr	3hr	1hr	2hr	3 hr	
39	139.4	8.17	135.4	132.2	128.3	4	7.2	11.1	202.4
37	124.0		119.8	115.6	114.2	4.2	8.4	9.8	203.4
19	155.1		151.4	150.4	149.2	3.7	4.7	5.9	222.3
6	158.1		153.1	149.5	148.0	5.0	8.6	10.1	200.1
25	146.7		144.2	138.3	135.8	2.5	8.4	10.9	235.9
24	103.5		102.5	98.5	98.2	1.0	5.0	5.3	211.2
3	99.9		98.4	94.3	92.4	1.5	5.6	7.5	222.3
26	141.0		135.3	132.0	131.3	5.7	9.0	9.7	218
X						3.4	7.1	8.5	216.2
sd						1.8	1.9	2.2	12.3

5 **Drug:**
(S,S)-6-(4-Amino-butyl)-1-biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-piperazine-2,5-dione (example 23) 10 mg/kg i.p.

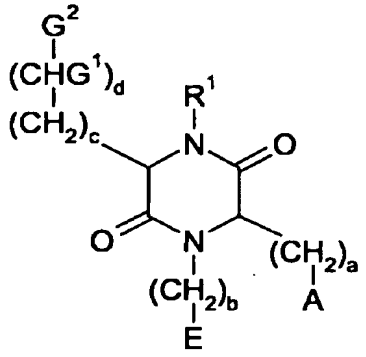
Diet Consumed, Grams

	Raw Data					Diet Consumed			Weight of RAT, g
Rat #	Diet in	Time in	1 hr	2 hr	3hr	1hr	2hr	3 hr	
27	111.5	8.35	104.8	103.6	100.8	6.7	7.9	10.7	234.7
36	151.2		148.7	144.9	144.9	2.5	6.3	6.3	234.7
34	153.6		153.4	149.0	147.8	.2	4.6	5.8	226.7
23	154.1		150.9	149.0	149.0	3.2	5.1	5.1	228
8	117.2		115.1	113.4	111.8	2.1	3.8	5.4	180.3
18	122.8		119.8	117.0	117.0	3.0	5.8	5.8	211.8
12	155.0		153.5	150.8	149.9	1.5	4.2	5.1	197.4
1	143.6		142.6	139.8	136.9	1.0	3.8	6.7	228
X						2.7	5.4	6.3	216.2
sd						2.0	1.4	2.0	20.8

These results are graphically represented in figure 1.

CLAIMS

1. A compound of the general formula (I)



Formula (I)

wherein

A is $-NR^2R^3$ or guanidinyl, the last optionally substituted with C_{1-6}-alkyl, wherein

R^2 and R^3 independently of each other are hydrogen, C_{1-6}-alkyl, C_{1-6}-alkylene-$N(R^{11})(R^{12})$, C_{1-6}-alkylene-CN, C_{1-6}-alkylene-OH, C_{1-6}-alkylene-$C(O)$-$N(R^{11})(R^{12})$, $(Z^1)_e$-R^{13}, or -CO-R^{14}, wherein

R^{11} and R^{12} independently of each other are hydrogen or C_{1-6}-alkyl;

Z^1 is C_{1-6}-alkylene;

e is an integer selected from 0 or 1;

R^{13} is cycloalkyl, heterocyclyl, aryl, or heteroaryl; each of which may be optionally substituted with a substitutent selected from the group consisting of C_{1-6}-alkyl, amino, and -CO-O-Z^4-R^{23}, wherein

Z^4 is C_{1-6}-alkylene; and

R^{23} is aryl; and

R^{14} is hydrogen, C_{1-6}-alkyl, $-N(R^{15})(R^{16})$, C_{1-6}-alkylene-$N(R^{15})(R^{16})$, $C(R^{17})(R^{18})$-$N(R^{19})(R^{20})$, heterocyclyl, $(Z^2)_f$-R^{21}, heteroaryl, or C_{1-6}-alkoxy, wherein

R^{15} and R^{16} independently of each other are hydrogen, or C_{1-6}-alkyl;

R^{17} and R^{18} independently of each other are hydrogen, C_{1-6}-alkylene-NH_2 or $(Z^3)_g$-R^{22}), wherein

Z^3 is C_{1-6}-alkylene;

g is an integer selected from 0 or 1; and

R^{22} is cycloalkyl, heterocyclyl, aryl or heteroaryl;

R^{19} and R^{20} independently of each other are hydrogen, C_{2-6}-alkylene-NH_2, C_{1-6}-alkylene-CF_3 or cycloalkyl; and

Z^2 is C_{1-6}-alkylene;

f is an integer selected from 0 or 1; and

R^{21} is cycloalkyl, heterocyclyl, aryl or heteroaryl;

a is an integer selected from 1, 2, 3, 4, or 5;

E is cycloalkyl, heterocyclyl, aryl or heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, $-NR^4R^5$, $-CO-R^6$, C_{1-6}-alkyl, C_{1-6}-alkoxy, trifluoromethyl, trifluoromethoxy, and $-L^1-Q^1$, wherein

R^4 and R^5 independently of each other are hydrogen, C_{1-6}-alkyl, $-CO-R^{24}$, or aryl, wherein

R^{24} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy;

R^6 is C_{1-6}-alkyl or C_{1-6}-alkoxy;

L^1 is a direct bond, $-CH_2-$, -O-, -CO-, $-CH_2-O-$, $-O-CH_2-$ or $-NR^{25}-$, wherein

R^{25} is hydrogen or C_{1-6}-alkyl; and

Q^1 is cycloalkyl, heterocyclyl, aryl or heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, $-NR^{26}R^{27}$, $-CO-R^{28}$, $-S(O)_2-R^{29}$, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl and C_{3-7}-cycloalkoxy, wherein

R^{26} and R^{27} independently of each other are hydrogen, C_{1-6}-alkyl, or $-CO-R^{30}$, wherein

R^{30} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy;

R^{28} is C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{29} is C_{1-6}-alkyl, $-NH-C_{1-6}$-alkyl, or $-N(C_{1-6}$-alkyl$)_2$;

or

Q^1 is L^3-R^{31}, wherein

L^3 is $-CH_2-$, -O-, -CO-, $-CH_2-O-$, $-O-CH_2-$, $-CH_2-O-C(O)-$, or $-C(O)-O-CH_2-$; and

R^{31} is aryl or heteroaryl;

b is an integer selected from 0, 1, or 2;

G^1 is C_{1-6}-alkyl, C_{1-6}-alkoxy, cycloalkyl, C_{3-7}-cycloalkoxy, aryl or heteroaryl; each of which may be optionally substituted with halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, $-NR^7R^8$, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkoxy, wherein

R^7 and R^8 independently of each other are hydrogen, C_{1-6}-alkyl, aryl, heteroaryl, $-CO-R^{32}$ or $-SO_2-R^{33}$, wherein

R^{32} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{33} is C_{1-6}-alkyl, $-NH-C_{1-6}$-alkyl, $-N(C_{1-6}$-alkyl$)_2$;

G^2 is cycloalkyl, heterocyclyl, aryl, or heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-NR^9R^{10}$, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkoxy or $-L^2-Q^2$, wherein

R^9 and R^{10} are independently hydrogen, C_{1-6}-alkyl, aryl, heteroaryl, $-CO-R^{34}$ or $-SO_2-R^{35}$, wherein

R^{34} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{35} is C_{1-6}-alkyl, $-NH-C_{1-6}$-alkyl, or $-N(C_{1-6}\text{-alkyl})_2$;

L^2 is a direct bond, $-CH_2-$, -O-, -CO-, $-CH_2-O-$, $-O-CH_2-$ or $-NR^{38}-$, wherein

R^{38} is hydrogen or C_{1-6}-alkyl; and

Q^2 is cycloalkyl, heterocyclyl, aryl or heteroaryl; each of which may be optionally substituted with halogen, hydroxy, cyano, nitro, trifluoromethyl, $-NR^{37}R^{38}$, $-CO-R^{39}$, $-O-R^{40}$, C_{1-6}-alkyl, C_{1-6}-hydroxyalkyl, C_{3-7}-cycloalkyl or C_{3-7}-cycloalkoxy, wherein

R^{37} and R^{38} independently of each other are hydrogen, C_{1-6}-alkyl or $-CO-R^{41}$, wherein

R^{41} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy;

R^{39} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{40} is C_{1-6}-alkyl or trifluoromethyl;

c is an integer selected from 0, 1, or 2;

d is an integer selected from 0, or 1;and

R^1 is hydrogen, alkyl, alkenyl, or alkynyl;

as well as any optical or geometric isomer or tautomer form thereof, or a pharmaeutically acceptable salt thereof.

2. A compound according to claim 1, wherein A is $-NR^2R^3$, wherein

R^2 and R^3 are as defined in claim 1.

3. A compound according to claim 1 or claim 2, wherein

R^2 is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkylene-$N(R^{11})(R^{12})$, C_{1-6}-alkylene-CN, C_{1-6}-alkylene-OH, C_{1-6}-alkylene-$C(O)-N(R^{11})(R^{12})$, $(Z^1)_e-R^{13}$, or $-CO-R^{14}$; and

R^3 is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkylene-$N(R^{11})(R^{12})$, $(Z^1)_e-R^{13}$, or $-CO-R^{14}$; wherein

R^{11}, R^{12}, Z^1, e, R^{13}, and R^{14} in each case are as defined in claim 1.

4. A compound according to claim 1 or claim 2, wherein

R^2 and R^3 independently of each other are hydrogen, C_{1-6}-alkyl, C_{1-6}-alkylene-$N(R^{11})(R^{12})$, $(Z^1)_e$-R^{13}, or -CO-R^{14}, wherein

R^{11}, R^{12}, Z^1, e, R^{13}, and R^{14} is as defined in claim 1.

5. A compound according to any of claims 1 to 4, wherein

R^{11} and R^{12} are hydrogen.

6. A compound according to claim 1 or claim 2, wherein

R^2 and R^3 independently of each other are hydrogen, C_{1-6}-alkyl, C_{1-6}-alkylene-CN, C_{1-6}-alkylene-OH, C_{1-6}-alkylene-$C(O)NH_2$, $(Z^1)_e$-R^{13}, or -CO-R^{14}, wherein

Z^1, e, R^{13}, and R^{14} are as defined in claim 1.

7. A compound according to any of claims 1 to 6, wherein

e is 1; and

Z^1 is $-CH_2-$.

8. A compound according to any of claims 1 to 7, wherein

R^{13} is cycloalkyl, or aryl; each of which may be optionally substituted with a substitutent selected from the group consisting of C_{1-6}-alkyl, amino, and -CO-O-Z^4-R^{23}, wherein

Z^4 and R^{23} is as defined in claim 1.

9. A compound according to claim 8, wherein

R^{13} is C_{3-7}-cycloalkyl, or C_{6-13}-aryl; each of which may be optionally substituted with a substitutent selected from the group consisting of C_{1-6}-alkyl, amino, and -CO-O-Z^4-R^{23}, wherein

Z^4 and R^{23} is as defined in claim 1.

10. A compound according to any of claims 1 to 7, wherein

R^{13} is heterocyclyl, or heteroaryl; each of which may be optionally substituted with a substitutent selected from the group consisting of C_{1-6}-alkyl, amino, and -CO-O-Z^4-R^{23}, wherein

Z^4 and R^{23} is as defined in claim 1.

11. A compound according to claim 10, wherein

R^{13} is C_{3-10}-heterocyclyl or C_{5-14}-heteroaryl; each of which may be optionally substituted with a substitutent selected from the group consisting of C_{1-6}-alkyl, amino, and -CO-O-Z^4-R^{23}, wherein

Z^4 and R^{23} is as defined in claim 1.

12. A compound according to any of claims 1 to 11, wherein R^{23} is C_{6-13}-aryl.

13. A compound according to claim 12, wherein R^{23} is phenyl.

14. A compound according to any of claims 1 to 13, wherein

R^2 and R^3 independently of each other are hydrogen, C_{1-6}-alkyl, or -CO-R^{14}, wherein

R^{14} is as defined in claim 1.

15. A compound according to any of claims 1 to 14, wherein

R^{14} is hydrogen, C_{1-6}-alkyl, -$NR^{15}R^{16}$, C_{1-6}-alkylene-$N(R^{15})(R^{16})$, $C(R^{17})(R^{18})$-$N(R^{19})(R^{20})$, C_{3-10}-heterocyclyl, $(Z^2)_f$-R^{21}, C_{5-14}-heteroaryl, or C_{1-6}-alkoxy, wherein

R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, Z^2, f, and R^{21} are as defined in claim 1.

16. A compound according to any of claims 1 to 15, wherein R^{15} and R^{16} are hydrogen.

17. A compound according to any of claims 1 to 16, wherein

R^{14} is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkylene-NH_2, $C(R^{17})(R^{18})$-$N(R^{19})(R^{20})$, C_{3-10}-heterocyclyl, $(Z^2)_f$-R^{21}, or C_{5-14}-heteroaryl, wherein

R^{17}, R^{18}, R^{19}, R^{20}, Z^2, f, and R^{21} are as defined in claim 1.

18. A compound according to claim 17, wherein

R^{14} is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkylene-NH_2, $C(R^{17})(R^{18})$-$N(R^{19})(R^{20})$, C_{5-6}-heterocyclyl, $(Z^2)_f$-R^{21}, or C_{5-6}-heteroaryl, wherein

R^{17}, R^{18}, R^{19}, R^{20}, Z^2, f, and R^{21} are as defined in claim 1.

19. A compound according to claim 18, wherein

R^{14} is hydrogen, C_{1-6}-alkyl, C_{1-6}-alkylene-NH_2, $C(R^{17})(R^{18})$-$N(R^{19})(R^{20})$, piperidinyl, $(Z^2)_f$-R^{21}, or pyridinyl, wherein

R^{17}, R^{18}, R^{19}, R^{20}, Z^2, f, and R^{21} are as defined in claim 1.

20. A compound according to any of claims 1 to 19, wherein

R^{17} and R^{18} independently of each other are hydrogen, C_{1-6}-alkylene-NH_2 or $(Z^3)_g$-R^{22}), wherein

Z^3 is -CH_2-; and

g is 1; and

R^{22} is as defined in claim 1.

21. A compound according to any of claims 1 to 20, wherein

R^{22} is C_{3-12}-cycloalkyl, C_{3-10}-heterocyclyl, C_{6-13}-aryl or C_{5-14}-heteroaryl.

22. A compound according to claim 21, wherein

R^{22} is C_{3-7}-cycloalkyl, C_{5-6}-heterocyclyl, C_{6-13}-aryl or C_{5-6}-heteroaryl.

23. A compound according to claim 22, wherein

R^{22} is C_{5-6}-heterocyclyl.

24. A compound according to any of claims 1 to 23, wherein

R^{17} and R^{18} are hydrogen.

25. A compound according to any of claims 1 to 24, wherein

R^{19} and R^{20} independently of each other are hydrogen, C_{2-6}-alkylene-NH_2, C_{1-6}-alkylene-CF_3 or C_{3-7}-cycloalkyl.

26. A compound according to claim 25, wherein

R^{19} and R^{20} are hydrogen.

27. A compound according to any of claims 1 to 26, wherein

f is 1;

Z^2 is -CH_2-; and

R^{21} is as defined in claim 1.

28. A compound according to any of claims 1 to 27, wherein

R^{21} is heterocyclyl or heteroaryl.

29. A compound according to claim 28, wherein

R^{21} is C_{3-10}-heterocyclyl or C_{5-14}-heteroaryl.

30. A compound according to claim 29, wherein
R^{21} is C_{5-6}-heterocyclyl or C_{5-6}-heteroaryl.

31. A compound according to claim 30, wherein
R^{21} is piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, or pyridinyl.

32. A compound according to claim 15, wherein
R^{14} is hydrogen, C_{1-6}-alkyl, $-NR^{15}R^{16}$, or C_{1-6}-alkoxy, wherein
R^{15} and R^{16} are as defined in claim 1.

33. A compound according to any of claims 1 to 32, wherein R^{15} and R^{16} are hydrogen.

34. A compound according to any of claims 1 to 33, wherein
R^2 and R^3 independently of each other are hydrogen or C_{1-6}-alkyl.

35. A compound according to claim 34, wherein
R^2 and R^3 are hydrogen.

36. A compound according to claim 1, wherein A is guanidinyl optionally substituted with C_{1-6}-alkyl.

37. A compound according to any of claims 1 to 36, wherein a is 1.

38. A compound according to any of claims 1 to 35 with the proviso that when A is $-NR^2R^3$ and R^2 and R^3 are hydrogen, then a is 4 or 5.

39. A compound according to any of claims 1 to 38, wherein the sum of the carbon and nitrogen atoms in the $-(CH_2)_a$-A group is at least 4.

40. A compound according to claim 39, wherein the sum of the carbon and nitrogen atoms in the $-(CH_2)_a$-A group is at least 5.

41. A compound according to any of claims 1 to 40, wherein a is 4.

42. A compound according to any of claims 1 to 40, wherein a is 5.

43. A compound according to claim 1 or claim 2, wherein

R^2 is C_{3-6}-alkyl, C_{3-6}-alkylene-$N(R^{11})(R^{12})$, C_{3-6}-alkylene-CN, C_{3-6}-alkylene-OH, C_{3-6}-alkylene-$C(O)$-$N(R^{11})(R^{12})$, $(Z^1)_e$-R^{13}, or -CO-R^{14}; and

R^3 is C_{3-6}-alkyl, C_{3-6}-alkylene-$N(R^{11})(R^{12})$, $(Z^1)_e$-R^{13}, or -CO-R^{14};

wherein

R^{11}, R^{12}, Z^1, e, and R^{13} in each case are as defined in claim 1, and

R^{14} is C_{2-6}-alkyl, C_{2-6}-alkylene-$N(R^{15})(R^{16})$, $C(R^{17})(R^{18})$-$N(R^{19})(R^{20})$, heterocyclyl, $(Z^2)_f$-R^{21}, heteroaryl, C_{2-6}-alkoxy, or -$N(R^{42})(R^{43})$, wherein

R^{15} and R^{16} independently of each other are hydrogen, or C_{1-6}-alkyl;

R^{17} and R^{18} independently of each other are hydrogen, C_{1-6}-alkylene-NH_2 or $(Z^3)_g$-R^{22}), wherein

Z^3 is C_{1-6}-alkylene;

g is an integer selected from 0 or 1; and

R^{22} is cycloalkyl, heterocyclyl, aryl or heteroaryl;

R^{19} and R^{20} independently of each other are hydrogen, C_{2-6}-alkylene-NH_2, C_{1-6}-alkylene-CF_3 or cycloalkyl; and

Z^2 is C_{1-6}-alkylene;

f is an integer selected from 0 or 1; and

R^{21} is cycloalkyl, heterocyclyl, aryl or heteroaryl; and

R^{42} and R^{43} independently of each other are C_{1-6}-alkyl.

44. A compound according to claim 1 or claim 2, wherein

R^2 and R^3 independently of each other are C_{3-6}-alkyl, C_{3-6}-alkylene-$N(R^{11})(R^{12})$, $(Z^1)_e$-R^{13}, or -CO-R^{14}, wherein

R^{11}, R^{12}, Z^1, e, and R^{13} in each case are as defined in claim 1, and

R^{14} is C_{2-6}-alkyl, C_{2-6}-alkylene-$N(R^{15})(R^{16})$, $C(R^{17})(R^{18})$-$N(R^{19})(R^{20})$, heterocyclyl, $(Z^2)_f$-R^{21}, heteroaryl, C_{2-6}-alkoxy, or -$N(R^{42})(R^{43})$, wherein

R^{15} and R^{16} independently of each other are hydrogen, or C_{1-6}-alkyl;

R^{17} and R^{18} independently of each other are hydrogen, C_{1-6}-alkylene-NH_2 or $(Z^3)_g$-R^{22}), wherein

Z^3 is C_{1-6}-alkylene;

g is an integer selected from 0 or 1; and

R^{22} is cycloalkyl, heterocyclyl, aryl or heteroaryl;

R^{19} and R^{20} independently of each other are hydrogen, C_{2-6}-alkylene-NH_2, C_{1-6}-alkylene-CF_3 or cycloalkyl; and
Z^2 is C_{1-6}-alkylene;
f is an integer selected from 0 or 1; and
R^{21} is cycloalkyl, heterocyclyl, aryl or heteroaryl; and
R^{42} and R^{43} independently of each other are C_{1-6}-alkyl.

45. A compound according to claim 43 or claim 44, wherein
R^{11} and R^{12} are hydrogen.

46. A compound according to claim 1 or claim 2, wherein
R^2 and R^3 independently of each other are C_{3-6}-alkyl, C_{3-6}-alkylene-CN, C_{3-6}-alkylene-OH, C_{3-6}-alkylene-C(O)-NH_2, $(Z^1)_e$-R^{13}, or -CO-R^{14}, wherein
Z^1, e, and R^{13} are as defined in claim 1, and
R^{14} is C_{2-6}-alkyl, C_{2-6}-alkylene-$N(R^{15})(R^{16})$, $C(R^{17})(R^{18})$-$N(R^{19})(R^{20})$, heterocyclyl, $(Z^2)_f$-R^{21}, heteroaryl, C_{2-6}-alkoxy, or -$N(R^{42})(R^{43})$, wherein
R^{15} and R^{16} independently of each other are hydrogen, or C_{1-6}-alkyl;
R^{17} and R^{18} independently of each other are hydrogen, C_{1-6}-alkylene-NH_2 or $(Z^3)_g$-R^{22}), wherein
Z^3 is C_{1-6}-alkylene;
g is an integer selected from 0 or 1; and
R^{22} is cycloalkyl, heterocyclyl, aryl or heteroaryl;
R^{19} and R^{20} independently of each other are hydrogen, C_{2-6}-alkylene-NH_2, C_{1-6}-alkylene-CF_3 or cycloalkyl; and
Z^2 is C_{1-6}-alkylene;
f is an integer selected from 0 or 1; and
R^{21} is cycloalkyl, heterocyclyl, aryl or heteroaryl; and
R^{42} and R^{43} independently of each other are C_{1-6}-alkyl.

47. A compound according to any of claims 43 to 46, wherein
e is 1; and
Z^1 is -CH_2-.

48. A compound according to any of claims 43 to 47, wherein

R^{13} is cycloalkyl, or aryl; each of which may be optionally substituted with a substitutent selected from the group consisting of C_{1-6}-alkyl, amino, and -CO-O-Z^4-R^{23}, wherein

Z^4 and R^{23} is as defined in claim 1.

49. A compound according to claim 48, wherein

R^{13} is C_{3-7}-cycloalkyl, or C_{6-13}-aryl; each of which may be optionally substituted with a substitutent selected from the group consisting of C_{1-6}-alkyl, amino, and -CO-O-Z^4-R^{23}, wherein

Z^4 and R^{23} is as defined in claim 1.

50. A compound according to any of claims 43 to 47, wherein

R^{13} is heterocyclyl, or heteroaryl; each of which may be optionally substituted with a substitutent selected from the group consisting of C_{1-6}-alkyl, amino, and -CO-O-Z^4-R^{23}, wherein

Z^4 and R^{23} is as defined in claim 1.

51. A compound according to claim 50, wherein

R^{13} is C_{3-10}-heterocyclyl or C_{5-14}-heteroaryl; each of which may be optionally substituted with a substitutent selected from the group consisting of C_{1-6}-alkyl, amino, and -CO-O-Z^4-R^{23}, wherein

Z^4 and R^{23} is as defined in claim 1.

52. A compound according to any of claims 43 to 51, wherein R^{23} is C_{6-13}-aryl.

53. A compound according to claim 52, wherein R^{23} is phenyl.

54. A compound according to any of claims 43 to 53, wherein

R^2 and R^3 independently of each other are C_{3-6}-alkyl, or -CO-R^{14}, wherein

R^{14} is as defined in claim 43.

55. A compound according to any of claims 43 to 54, wherein

R^{14} is C_{2-6}-alkyl, C_{2-6}-alkylene-N(R^{15})(R^{16}), C(R^{17})(R^{18})-N(R^{19})(R^{20}), C_{3-10}-heterocyclyl, $(Z^2)_f$-R^{21}, C_{5-14}-heteroaryl, C_{2-6}-alkoxy, or -N(R^{42})(R^{43}), wherein

R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, Z^2, f, R^{21}, R^{42} and R^{43} are as defined in claim 43.

56. A compound according to any of claims 43 to 55, wherein R^{15} and R^{16} are hydrogen.

57. A compound according to any of claims 43 to 56, wherein

R^{14} is C_{2-6}-alkyl, C_{2-6}-alkylene-NH_2, $C(R^{17})(R^{18})$-$N(R^{19})(R^{20})$, C_{3-10}-heterocyclyl, $(Z^2)_f$-R^{21}, or C_{5-14}-heteroaryl, wherein

R^{17}, R^{18}, R^{19}, R^{20}, Z^2, f, and R^{21} are as defined in claim 43.

58. A compound according to claim 57, wherein

R^{14} is C_{2-6}-alkyl, C_{2-6}-alkylene-NH_2, $C(R^{17})(R^{18})$-$N(R^{19})(R^{20})$, C_{5-6}-heterocyclyl, $(Z^2)_f$-R^{21}, or C_{5-6}-heteroaryl, wherein

R^{17}, R^{18}, R^{19}, R^{20}, Z^2, f, and R^{21} are as defined in claim 43.

59. A compound according to claim 58, wherein

R^{14} is C_{2-6}-alkyl, C_{2-6}-alkylene-NH_2, $C(R^{17})(R^{18})$-$N(R^{19})(R^{20})$, piperidinyl, $(Z^2)_f$-R^{21}, or pyridinyl, wherein

R^{17}, R^{18}, R^{19}, R^{20}, Z^2, f, and R^{21} are as defined in claim 43.

60. A compound according to any of claims 43 to 59, wherein

R^{17} and R^{18} independently of each other are hydrogen, C_{1-6}-alkylene-NH_2 or $(Z^3)_g$-R^{22}), wherein

Z^3 is -CH_2-; and

g is 1; and

R^{22} is as defined in claim 43.

61. A compound according to any of claims 43 to 60, wherein

R^{22} is C_{3-12}-cycloalkyl, C_{3-10}-heterocyclyl, C_{6-13}-aryl or C_{5-14}-heteroaryl.

62. A compound according to claim 61, wherein

R^{22} is C_{3-7}-cycloalkyl, C_{5-6}-heterocyclyl, C_{6-13}-aryl or C_{5-6}-heteroaryl.

63. A compound according to claim 62, wherein

R^{22} is C_{5-6}-heterocyclyl.

64. A compound according to any of claims 43 to 63, wherein

R^{17} and R^{18} are hydrogen.

65. A compound according to any of claims 43 to 64, wherein

R^{19} and R^{20} independently of each other are hydrogen, C_{2-6}-alkylene-NH_2, C_{1-6}-alkylene-CF_3 or C_{3-7}-cycloalkyl.

66. A compound according to claim 65, wherein

R^{19} and R^{20} are hydrogen.

67. A compound according to any of claims 43 to 66, wherein

f is 1;

Z^2 is -CH_2-; and

R^{21} is as defined in claim 43.

68. A compound according to any of claims 43 to 67, wherein

R^{21} is heterocyclyl or heteroaryl.

69. A compound according to claim 68, wherein

R^{21} is C_{3-10}-heterocyclyl or C_{5-14}-heteroaryl.

70. A compound according to claim 69, wherein

R^{21} is C_{5-6}-heterocyclyl or C_{5-6}-heteroaryl.

71. A compound according to claim 70, wherein

R^{21} is piperidinyl, morpholinyl, imidazolyl, pyrrolidinyl, or pyridinyl.

72. A compound according to claim 56, wherein

R^{14} is hydrogen, C_{1-6}-alkyl, -$N(R^{15})(R^{16})$, or C_{1-6}-alkoxy, wherein

R^{15} and R^{16} are as defined in claim 43.

73. A compound according to any of claims 43 to 72, wherein R^{15} and R^{16} are hydrogen.

74. A compound according to any of claims 43 to 73, wherein

R^2 and R^3 independently of each other are C_{3-6}-alkyl.

75. A compound according to any of claims 43 to 74, wherein a is 1.

76. A compound according to any of claims 1 to 75, wherein

E is C_{3-12}-cycloalkyl, C_{3-10}-heterocyclyl, C_{6-13}-aryl or C_{5-14}-heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, $-NR^4R^5$, $-CO-R^6$, C_{1-6}-alkyl, C_{1-6}-alkoxy, trifluoromethyl, trifluoromethoxy, and $-L^1-Q^1$, wherein

R^4, R^5, R^6, L^1, and Q^1 are as defined in claim 1.

77. A compound according to any of claims 1 to 42, wherein

E is aryl or heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, $-NR^4R^5$, $-CO-R^6$, C_{1-6}-alkyl, C_{1-6}-alkoxy, trifluoromethyl, trifluoromethoxy, and $-L^1-Q^1$, wherein

R^4, R^5, R^6, L^1, and Q^1 are as defined in claim 1.

78. A compound according to claim 76 or claim 77, wherein

E is C_{6-13}-aryl or C_{5-14}-heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, $-NR^4R^5$, $-CO-R^6$, C_{1-6}-alkyl, C_{1-6}-alkoxy, trifluoromethyl, trifluoromethoxy, and $-L^1-Q^1$, wherein

R^4, R^5, R^6, L^1, and Q^1 are as defined in claim 1.

79. A compound according to claim 78, wherein

E is C_{6-13}-aryl or C_{5-14}-heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, $-NR^4R^5$, C_{1-6}-alkyl, C_{1-6}-alkoxy, and $-L^1-Q^1$, wherein

R^4, R^5, L^1, and Q^1 are as defined in claim 1.

80. A compound according to any of claims 1 to 79, wherein

R^4 and R^5 independently of each other are hydrogen, C_{1-6}-alkyl, or aryl.

81. A compound according to claim 80, wherein

R^4 and R^5 independently of each other are hydrogen, C_{1-6}-alkyl, or C_{6-13}-aryl.

82. A compound according to claim 81, wherein

R^4 and R^5 independently of each other are hydrogen, C_{1-6}-alkyl, or phenyl.

83. A compound according to any of claims 1 to 82, wherein

L^1 is a direct bond, $-CH_2-$, -O-, $-CH_2-O-$, or $-O-CH_2-$.

84. A compound according to claim 83, wherein

L^1 is a direct bond.

85. A compound according to claim 83, wherein

L^1 is $-CH_2-$.

86. A compound according to claim 83, wherein

L^1 is -O-.

87. A compound according to any of claims 1 to 86, wherein

Q^1 is C_{3-12}-cycloalkyl, C_{3-10}-heterocyclyl, C_{6-13}-aryl, or C_{5-14}-heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, $-NR^{26}R^{27}$, $-CO-R^{28}$, $-S(O)_2-R^{29}$, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl and C_{3-7}-cycloalkoxy, wherein

R^{26}, R^{27}, R^{28}, and R^{29} are as defined in claim 1.

88. A compound according to claim 87, wherein

Q^1 is C_{3-7}-cycloalkyl, C_{5-6}-heterocyclyl, C_{6-13}-aryl, or C_{5-6}-heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, $-NR^{26}R^{27}$, $-CO-R^{28}$, $-S(O)_2-R^{29}$, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl and C_{3-7}-cycloalkoxy, wherein

R^{26}, R^{27}, R^{28}, and R^{29} are as defined in claim 1.

89. A compound according to claim 88, wherein

Q^1 is C_{3-7}-cycloalkyl, or C_{6-13}-aryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, $-NR^{26}R^{27}$, $-CO-R^{28}$, $-S(O)_2-R^{29}$, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl and C_{3-7}-cycloalkoxy, wherein

R^{26}, R^{27}, R^{28}, and R^{29} are as defined in claim 1.

90. A compound according to claim 89, wherein

Q^1 is C_{5-8}-cycloalkyl, or C_{6-10}-aryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, $-NR^{26}R^{27}$, $-CO-R^{28}$, $-S(O)_2-R^{29}$, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl and C_{3-7}-cycloalkoxy, wherein

R^{26}, R^{27}, R^{28}, and R^{29} are as defined in claim 1.

91. A compound according to claim 90, wherein

Q^1 is phenyl or cyclohexyl, which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, $-NR^{26}R^{27}$, $-CO-R^{28}$, $-S(O)_2-R^{29}$, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl and C_{3-7}-cycloalkoxy, wherein

R^{26}, R^{27}, R^{28}, and R^{29} are as defined in claim 1.

92. A compound according to any of claims 1 to 91, wherein

R^{26} and R^{27} independently of each other are hydrogen, or C_{1-6}-alkyl.

93. A compound according to claim 92, wherein

R^{26} and R^{27} independently of each other are hydrogen, or methyl.

94. A compound according to any of claims 1 to 93, wherein

R^{28} is methyl.

95. A compound according to any of claims 1 to 94, wherein

R^{29} is C_{1-6}-alkyl.

96. A compound according to claim 95, wherein

R^{29} is methyl.

97. A compound according to any of claims 1 to 86, wherein

Q^1 is L^3-R^{31}, wherein

L^3 is $-CH_2-$, $-CH_2-O-C(O)-$, or $-C(O)-O-CH_2-$; and

R^{31} is as defined in claim 1.

98. A compound according to any of claims 1 to 97, wherein

R^{31} is C_{6-13}-aryl or C_{3-10}-heteroaryl.

99. A compound according to claim 98, wherein

R^{31} is C_{6-10}-aryl or C_{5-6}-heteroaryl.

100. A compound according to claim 99, wherein

R^{31} is phenyl.

101. A compound according to any of claims 1 to 100, wherein b is 1.

102. A compound according to any of claims 1 to 101, wherein c is 1.

103. A compound according to any of claims 1 to 102, wherein d is 0.

104. A compound according to any of claims 1 to 103, wherein

G^2 is C_{3-12}-cycloalkyl, C_{3-10}-heterocyclyl, C_{6-13}-aryl or C_{5-14}-heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-NR^9R^{10}$, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkoxy or $-L^2-Q^2$, wherein

R^9, R^{10}, L^2, and Q^2 are as defined in claim 1.

105. A compound according to any of claims 1 to 103, wherein

G^2 is aryl or heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-NR^9R^{10}$, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkoxy or $-L^2-Q^2$, wherein

R^9, R^{10}, L^2, and Q^2 are as defined in claim 1.

106. A compound according to claim 104 or claim 105, wherein

G^2 is C_{6-13}-aryl or C_{5-14}-heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-NR^9R^{10}$, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkoxy or $-L^2-Q^2$, wherein

R^9, R^{10}, L^2, and Q^2 are as defined in claim 1.

107. A compound according to claim 106, wherein

G^2 is C_{6-10}-aryl or C_{5-10}-heteroaryl; each of which may be optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, $-NR^9R^{10}$, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{3-7}-cycloalkyl, C_{3-7}-cycloalkoxy or $-L^2$-Q^2, wherein

R^9, R^{10}, L^2, and Q^2 are as defined in claim 1.

108. A compound according to any of claims 1 to 107, wherein

R^9 and R^{10} are independently hydrogen, C_{1-6}-alkyl, C_{6-13}-aryl, C_{5-14}-heteroaryl, $-CO-R^{34}$ or $-SO_2-R^{35}$, wherein

R^{34} and R^{35} are as defined in claim 1.

109. A compound according to claim 108, wherein

R^{34} is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy; and

R^{35} is C_{1-6}-alkyl.

110. A compound according to claim 109, wherein

R^9 and R^{10} are hydrogen.

111. A compound according to any of claims 1 to 110, wherein

L^2 is a direct bond, $-CH_2-$, -O-, -CO-, $-CH_2-O-$, $-O-CH_2-$ or $-NR^{38}-$, wherein

R^{38} is hydrogen or methyl.

112. A compound according to any of claims 1 to 111, wherein

L^2 is a direct bond, $-CH_2-$, -O-, -CO-, $-CH_2-O-$, or $-O-CH_2-$.

113. A compound according to any of claims 1 to 112, wherein

Q^2 is C_{3-12}-cycloalkyl, C_{3-10}-heterocyclyl, C_{6-13}-aryl or C_{5-14}-heteroaryl; each of which may be optionally substituted with halogen, hydroxy, cyano, nitro, trifluoromethyl, $-NR^{37}R^{38}$, $-CO-R^{39}$, $-O-R^{40}$, C_{1-6}-alkyl, C_{1-6}-hydroxyalkyl, C_{3-7}-cycloalkyl or C_{3-7}-cycloalkoxy, wherein

R^{37}, R^{38}, R^{39}, and R^{40} are as defined in claim 1.

114. A compound according to claim 113, wherein

Q^2 is C_{3-12}-cycloalkyl, C_{3-10}-heterocyclyl, C_{6-13}-aryl or C_{5-14}-heteroaryl; each of which may be optionally substituted with halogen, hydroxy, cyano, nitro, trifluoromethyl, $-NR^{37}R^{38}$, $-CO-R^{39}$, $-O-R^{40}$, C_{1-6}-alkyl, or C_{1-6}-hydroxyalkyl, wherein

R^{37}, R^{38}, R^{39}, and R^{40} are as defined in claim 1.

115. A compound according to claim 113, wherein

Q^2 is C_{3-7}-cycloalkyl, C_{5-6}-heterocyclyl, C_{6-13}-aryl or C_{5-6}-heteroaryl; each of which may be optionally substituted with halogen, hydroxy, cyano, nitro, trifluoromethyl, $-NR^{37}R^{38}$, $-CO-R^{39}$, $-O-R^{40}$, C_{1-6}-alkyl, C_{1-6}-hydroxyalkyl, C_{3-7}-cycloalkyl or C_{3-7}-cycloalkoxy, wherein

R^{37}, R^{38}, R^{39}, and R^{40} are as defined in claim 1.

116. A compound according to claim 115, wherein

Q^2 is C_{3-7}-cycloalkyl, C_{5-6}-heterocyclyl, C_{6-13}-aryl or C_{5-6}-heteroaryl; each of which may be optionally substituted with halogen, hydroxy, cyano, nitro, trifluoromethyl, $-NR^{37}R^{38}$, $-CO-R^{39}$, $-O-R^{40}$, C_{1-6}-alkyl, or C_{1-6}-hydroxyalkyl, wherein

R^{37}, R^{38}, R^{39}, and R^{40} are as defined in claim 1.

117. A compound according to any of claims 1 to 116, wherein

R^{37} and R^{38} independently of each other are hydrogen or C_{1-6}-alkyl.

118. A compound according to claim 117, wherein

R^{37} and R^{38} independently of each other are hydrogen or methyl.

119. A compound according to any of claims 1 to 118, wherein

R^{39} is hydrogen or C_{1-6}-alkyl.

120. A compound according to claim 119, wherein

R^{39} is hydrogen or methyl.

121. A compound according to any of claims 1 to 120, wherein

R^{40} is trifluoromethyl.

122. A compound according to any of claims 1 to 121, wherein

R^1 is hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, or C_{2-6}-alkynyl.

123. A compound according to claim 122, wherein

R^1 is hydrogen.

124. A compound according to claim 1, where the compound is
(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,,
(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-naphthalen-1-ylmethyl-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-3-(4-benzyloxy-benzyl)-1-biphenyl-4-ylmethyl-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1,3-bis-biphenyl-4-ylmethyl-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-3-naphthalen-2-ylmethyl-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-3-benzo[b]thiophen-3-ylmethyl-1-biphenyl-4-ylmethyl-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-3-(4-benzoyl-benzyl)-1-biphenyl-4-ylmethyl-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-(4'-methoxy-biphenyl-4-ylmethyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-3-naphthalen-2-ylmethyl-1-(4'-trifluoromethyl-biphenyl-4-ylmethyl)-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-(4'-chloro-biphenyl-4-ylmethyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-(9*H*-fluoren-2-ylmethyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,
(*S,S*)-4'-[2-(4-amino-butyl)-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-ylmethyl]-biphenyl-2-carboxylic acid methyl,
(*S,S*)-6-(4-amino-butyl)-3-(4-benzoyl-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-3-(4-methoxy-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-3-(4-chloro-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-3-(4-methyl-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,
(*S,S*)-4'-[2-(4-amino-butyl)-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-1-ylmethyl]-biphenyl-2-carbonitrile,
(*S,S*)-6-(4-amino-butyl)-1-(4-cyclohexyloxy-benzyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-3-naphthalen-2-ylmethyl-1-[4-(3-trifluoromethyl-cyclohexyloxy)-benzyl]-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-(4-cyclohexyl-benzyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,
(*S,S*)-1-biphenyl-4-ylmethyl-6-(4-dimethylamino-butyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,
(*S,S*)-1-biphenyl-4-ylmethyl-6-(4-methylamino-butyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-3-(4-ethoxy-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-propoxy-benzyl)-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-isopropoxy-benzyl)-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-(4-phenoxy-benzyl)-3-(4-pyrrol-1-yl-benzyl)-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-cyclopropylmethoxy-benzyl)-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-cyclohexyloxy-benzyl)-piperazine-2,5-dione,
(*S,S*)-1-biphenyl-4-ylmethyl-6-(4-isopropylamino-butyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-phenoxy-benzyl)-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-m-tolyloxy-benzyl)-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(4-methoxy-phenoxy)-benzyl]-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-[4-(4-dimethylamino-phenoxy)-benzyl]-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-[4-(4-methoxy-phenoxy)-benzyl]-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,
(*S,S*)-1-[4-(3-acetyl-phenoxy)-benzyl]-6-(4-amino-butyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-[4-(4-ethanesulfonyl-phenoxy)-benzyl]-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(4-chloro-phenoxy)-benzyl]-piperazine-2,5-dione,
(*S,S*)-3-[4-(4-acetyl-phenoxy)-benzyl]-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-piperazine-2,5-dione,
(*S,S*)-3-[4-(3-acetyl-phenoxy)-benzyl]-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-methoxy-benzyl)-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-(4-ethoxy-benzyl)-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(3-trifluoromethoxy-phenoxy)-benzyl]-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(4-fluoro-phenoxy)-benzyl]-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(3-nitro-phenoxy)-benzyl]-piperazine-2,5-dione,
(*S,S*)-6-(4-amino-butyl)-1-(4-phenoxy-benzyl)-3-(4-propoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(pyridin-3-yloxy)-benzyl]-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(4-dimethylamino-phenoxy)-benzyl]-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-3-naphthalen-2-ylmethyl-1-(6-phenyl-pyridin-3-ylmethyl)-piperazine-2,5-dione,

(*S,S*)-3-{4-[5-(4-amino-butyl)-4-biphenyl-4-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl]-phenoxy}-benzaldehyde,

(*S,S*)-6-(4-amino-butyl)-1-(4-bromo-benzyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-3-(4-isopropoxy-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-6-[4-(2-amino-ethylamino)-butyl]-1-(4-phenoxy-benzyl)-3-(4-propoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-3-amino-*N*-(1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-3-methyl-*N*-piperidin-4-ylmethyl-butyramide,

(*S,S*)-3-amino-*N*-(1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-*N*-pyridin-4-ylmethyl-propionamide,

(*S,S*)-3-amino-*N*-[5-(4-ethoxy-benzyl)-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-3-methyl-*N*-piperidin-4-ylmethyl-butyramide,

(*S,S*)-3-amino-*N*-[5-(4-ethoxy-benzyl)-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-*N*-piperidin-4-ylmethyl-propionamide,

(*S,S*)-6-{[bis-(3*H*-imidazol-4-ylmethyl)-amino]-methyl}-3-(4-ethoxy-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-3-amino-*N*-(2-amino-2-methyl-propyl)-*N*-[5-(4-ethoxy-benzyl)-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-3-methyl-butyramide,

(*S,S*)-1-[4-(4-acetyl-phenoxy)-benzyl]-6-(4-amino-butyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(*S,S*)-6-(4-amino-butyl)-1-biphenyl-4-ylmethyl-3-[4-(3-hydroxymethyl-phenoxy)-benzyl]-piperazine-2,5-dione,

(*S,S*)-6-{4-[(1*H*-imidazol-2-ylmethyl)-amino]-butyl}-3-(4-methoxy-benzyl)-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

(*S,S*)-3-(4-methoxy-benzyl)-1-(4-phenoxy-benzyl)-6-{4-[(pyridin-2-ylmethyl)-amino]-butyl}-piperazine-2,5-dione,

(*2R,2'S,5'S*)-2-amino-*N*-[5-(4-ethoxy-benzyl)-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-3-(1*H*-imidazol-4-yl)-propionamide,

(*S,S*)-2-(3-amino-propylamino)-*N*-[1-[4-(methyl-phenyl-amino)-benzyl]-3,6-dioxo-5-(4-propoxy-benzyl)-piperazin-2-ylmethyl]-acetamide,

N-[4-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-yl)-butyl]-acetamide,

(3*S*,6*S*)-1-biphenyl-4-ylmethyl-6-(4-dimethylamino-butyl)-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

N-[4-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-yl)-butyl]-guanidine hydrochloride,

(3*S*,6*S*)-6-[4-(3-amino-pyridin-2-ylamino)-butyl]-3-naphthalen-2-ylmethyl-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

{4-[(2*S*,5*S*)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-yl]-butylamino}-acetonitrile,

N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-acetamide,

(3*S*,6*S*)-1-biphenyl-4-ylmethyl-6-[(cyclohexylmethyl-piperidin-4-ylmethyl-amino)-methyl]-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(3*S*,6*S*)-1-biphenyl-4-ylmethyl-6-[(ethyl-piperidin-4-ylmethyl-amino)-methyl]-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(3*S*,6*S*)-1-biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-6-[(piperidin-4-ylmethyl-pyridin-4-ylmethyl-amino)-methyl]-piperazine-2,5-dione,

3-amino-N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-propionamide,

4-{[((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-(piperidine-4-carbonyl)-amino]-methyl}-piperidine-1-carboxylic acid benzyl ester,

4-{[((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-((*R*,*S*)-piperidine-3-carbonyl)-amino]-methyl}-piperidine-1-carboxylic acid benzyl ester,

piperidine-4-carboxylic acid ((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-piperidin-4-ylmethyl-amide,

(*R*,*S*)-piperidine-3-carboxylic acid ((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-piperidin-4-ylmethyl-amide,

4-amino-N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-butyramide,

(3*S*,6*S*)-6-{[(3-amino-propyl)-piperidin-4-ylmethyl-amino]-methyl}-1-biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

1H-imidazole-4-carboxylic acid [(2*S*,5*S*)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-piperidin-4-ylmethyl-amide,

2-amino-N-[(2*S*,5*S*)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-N-piperidin-4-ylmethyl-acetamide,

3-amino-N-[(2*S*,5*S*)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-N-piperidin-4-ylmethyl-propionamide,

N-[(2*S*,5*S*)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-2-piperidin-4-yl-N-piperidin-4-ylmethyl-acetamide,

(*R*,*S*)-2,5-diamino-pentanoic acid [(2*S*,5*S*)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-piperidin-4-ylmethyl-amide,

(3*S*,6*S*)-6-{[(3-dimethylamino-propyl)-piperidin-4-ylmethyl-amino]-methyl}-3-naphthalen-2-ylmethyl-1-(4-phenoxy-benzyl)-piperazine-2,5-dione,

3-amino-N-(1-methyl-piperidin-4-ylmethyl)-N-[(2*S*,5*S*)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-propionamide,

piperidine-3-carboxylic acid [(2*S*,5*S*)-5-naphthalen-2-ylmethyl-3,6-dioxo-1-(4-phenoxy-benzyl)-piperazin-2-ylmethyl]-piperidin-4-ylmethyl-amide,

(3*S*,6*S*)-1-biphenyl-4-ylmethyl-6-{[bis-(1-methyl-piperidin-4-ylmethyl)-amino]-methyl}-3-naphthalen-2-ylmethyl-piperazine-2,5-dione,

(3*S*,6*S*)-6-{[(3-amino-propyl)-piperidin-4-ylmethyl-amino]-methyl}-1-(4-phenoxy-benzyl)-3-(4-trifluoromethyl-benzyl)-piperazine-2,5-dione,

(3*S*,6*S*)-6-{[(3-hydroxy-propyl)-piperidin-4-ylmethyl-amino]-methyl}-1-(4-phenoxy-benzyl)-3-(4-trifluoromethyl-benzyl)-piperazine-2,5-dione,

3-amino-N-[(2*S*,5*S*)-3,6-dioxo-1-(4-phenoxy-benzyl)-5-(4-trifluoromethyl-benzyl)-piperazin-2-ylmethyl]-N-piperidin-4-ylmethyl-propionamide,

N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-2-(*R*,*S*)-morpholin-2-yl-N-piperidin-4-ylmethyl-acetamide,

(3*S*,6*S*)-1-biphenyl-4-ylmethyl-3-naphthalen-2-ylmethyl-6-[(piperidin-4-ylmethyl-pyridin-3-ylmethyl-amino)-methyl]-piperazine-2,5-dione,

(3*S*,6*S*)-1-(4-phenoxy-benzyl)-6-[(piperidin-4-ylmethyl-pyridin-3-ylmethyl-amino)-methyl]-3-(4-trifluoromethyl-benzyl)-piperazine-2,5-dione,

N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-2-cyclopropylamino-N-piperidin-4-ylmethyl-acetamide,

N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-2-(2,2,2-trifluoro-ethylamino)-acetamide,

N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-2-imidazol-1-yl-N-piperidin-4-ylmethyl-acetamide,

2-[((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-piperidin-4-ylmethyl-amino]-acetamide,

N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-2-pyridin-3-yl-acetamide,

N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-nicotinamide,
N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-piperidin-4-ylmethyl-2-pyrrolidin-1-yl-acetamide, or
3-amino-N-((2*S*,5*S*)-1-biphenyl-4-ylmethyl-5-naphthalen-2-ylmethyl-3,6-dioxo-piperazin-2-ylmethyl)-N-pyridin-3-ylmethyl-propionamide.

125. A compound according to any of claims 1 to 124, wherein the compound is an agonist of the MC4 receptor.

126. A compound according to claim 125, wherein the compound is selective for the MC4 receptor.

127. A pharmaceutical composition comprising a compound according to any of claims 1 to 126.

128. Use of a compound according to any of claims 1 to 126 for the preparation of a medicament.

129. Use of a compound according to any of claims 1 to 126 for increasing the activity of the MC4 receptor.

130. Use of a compound according to any of claims 1 to 126 for the delaying or prevention of the progression from IGT to type 2 diabetes.

131. Use of a compound according to any of claims 1 to 126 for the preparation of a medicament for the delaying or prevention of the progression from IGT to type 2 diabetes.

132. Use of a compound according to any of claims 1 to 126 for the delaying or prevention of the progression from non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes.

133. Use of a compound according to any of claims 1 to 126 for the preparation of a medicament for the delaying or prevention of the progression from non-insulin requiring type 2 diabetes to insulin requiring type 2 diabetes.

134. Use of a compound according to any of claims 1 to 126 for appetite regulation.

135. Use of a compound according to any of claims 1 to 126 for treating a condition which is improved by the activation of the MC4 receptor.

136. Use of a compound according to any of claims 1 to 126 for the preparation of a medicament for treating a condition which is improved by the activation of the MC4 receptor.

137. Use of a compound according to any of claims 1 to 126 for the preparation of a medicament for appetite regulation.

138. Use according to claim 135 or claim 136, where the condition to be treated is a disease or condition related to overweight or obesity.

139. Use according to claim 135 or claim 136, where the condition to be treated is a disease or condition selected from overweight or obesity, atherosclerosis, hypertension, diabetes, type 2 diabetes, impaired glucose tolerance, dyslipidaemia, coronary heart disease, gallbladder disease, osteoarthritis, cancer, sexual dysfunction and the risk for premature death in a patient in need thereof.

140. Use according to claim 139, wherein the disease is overweight or obesity.

141. Use according to claim 139, wherein the disease is type 2 diabetes.

142. Use according to claim 141, wherein the patient in need thereof is obese.

143. Use according to claim 139, wherein the disease is dyslipidemia.

144. Use according to claim 143, wherein the patient in need thereof is obese.

145. Use according to claim 139, wherein the condition is sexual dysfunction.

146. Use of a compound according to any of claims 1 to 126 for reducing the weight of a subject.

147. Use of a compound according to any of claims 1 to 126 for the preparation of a medicament for reducing the weight of a subject.

148. Use according to claim 146 or claim 147, wherein the subject is a mammal.

149. Use according to claim 148, wherein the subject is a human.

150. Use of a compound according to any of claims 1 to 126 for the suppression of appetite or for satiety induction.

151. Use of a compound according to any of claims 1 to 126 for the preparation of a medicament for the suppression of appetite or for satiety induction.

152. Use of a compound according to any of claims 1 to 126 for treatment of eating disorders such as bulimia and binge eating.

153. Use of a compound according to any of claims 1 to 126 for the preparation of a medicament for treatment of eating disorders such as bulimia and binge eating.

154. A method for the treatment of a condition which is improved by the activation of the MC4 receptor, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 126.

155. A method for the treatment of hyperglycemia, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 126.

156. A method for the treatment of IGT, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 126.

157. A method for the treatment of Syndrome X, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 126.

158. A method for the treatment of type 2 diabetes, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 126.

159. A method for the treatment of type 1 diabetes, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 126.

160. A method for the treatment of dyslipidemia or hyperlipidemia, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 126.

161. A method for the treatment of sexual dysfunction, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 126.

162. A method for reducing the weight of a subject, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 126.

163. A method for the suppression of appetite or for satiety induction, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 126.

164. A method for treatment of eating disorders such as bulimia and binge eating, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 126.

165. A method for treating a disease or condition related to overweight or obesity, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 126.

166. A method for the treatment of overweight or obesity, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 126.

167. A method according to any of claims 155 to 166, wherein the therapeutically effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, such as from about 0.1 mg to about 1000 mg, for example from about 0.5 mg to about 500 mg per day.

168. A method according to any of claims 155 to 167 in a regimen which comprises treatment with a further antidiabetic agent.

169. A method according to any of claims 155 to 168 in a regimen which comprises treatment with a further antihyperlipidemic agent.

170. A method according to any of claims 155 to 169 in a regimen which comprises treatment with a further antiobesity agent.

171. A method according to any of claims 155 to 170 in a regimen which comprises treatment with a further antihypertensive agent.

172. A compound according to any of claims 1 to 123, where the compound is an agonist of the MC1 receptor.

173. A compound according to claim 172, wherein the compound is selective for the MC1 receptor.

174. A pharmaceutical composition comprising a compound according to claim 172 or claim 173.

175. Use of a compound according to any of claims 1 to 123 or claim 172 or claim 173 for increasing the activity of the MC1 receptor.

176. Use of a compound according to any of claims 1 to 123 or claim 172 or claim 173 for treating a condition which is improved by the activation of the MC1 receptor.

177. Use of a compound according to any of claims 1 to 123 or claim 172 or claim 173 for the preparation of a medicament for treating a condition which is improved by the activation of the MC1 receptor.

178. Use of a compound according to any of claims 1 to 123 or claim 172 or claim 173 for increasing skin pigmentation, for protecting the skin against ultraviolet radiation (UVR), for inhibiting the effects of UVR, for protecting the skin against local skin irritants, for modulating the inflammatory responses in the skin, for functionally antagonising the actions of proinflammatory cytokines produced in the skin after a local irritation, for regulating the immune response, for preventing contact dermatitis, or for inhibiting chronic inflammatory responses.

179. Use of a compound according to any of claims 1 to 123 or claim 172 or claim 173 for the preparation of a medicament for increasing skin pigmentation, for protecting the skin against ultraviolet radiation (UVR), for inhibiting the effects of UVR, for protecting the skin against local skin irritants, for modulating the inflammatory responses in the skin, for functionally antagonising the actions of proinflammatory cytokines produced in the skin after a local irritation, for regulating the immune response, for preventing contact dermatitis, or for inhibiting chronic inflammatory responses.

180. A method for the treatment of a condition which is improved by the activation of the MC1 receptor, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 123 or claim 172 or claim 173.

181. A method for increasing skin pigmentation, for protecting the skin against ultraviolet radiation (UVR), for inhibiting the effects of UVR, for protecting the skin against local skin irritants, for modulating the inflammatory responses in the skin, for functionally antagonising the actions of proinflammatory cytokines produced in the skin after a local irritation, for regulating the immune response, for preventing contact dermatitis, or for inhibiting chronic inflammatory responses, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 123 or claim 172 or claim 173.

182. A method according to claim 180 or claim 181, wherein the therapeutically effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, such as from about 0.1 mg to about 1000 mg, for example from about 0.5 mg to about 500 mg per day.

183. A compound according to any of claims 1 to 123, where the compound is an agonist of the MC2 receptor.

184. A compound according to claim 183, wherein the compound is selective for the MC2 receptor.

185. A pharmaceutical composition comprising a compound according to claim 183 or claim 184.

186. Use of a compound according to any of claims 1 to 123 or claim 183 or claim 184 for increasing the activity of the MC2 receptor.

187. Use of a compound according to any of claims 1 to 123 or claim 183 or claim 184 for treating a condition which is improved by the activation of the MC2 receptor.

188. Use of a compound according to any of claims 1 to 123 or claim 183 or claim 184 for the preparation of a medicament for treating a condition which is improved by the activation of the MC2 receptor.

189. Use of a compound according to any of claims 1 to 123 or claim 183 or claim 184 for regulating glucocorticoid production.

190. Use of a compound according to any of claims 1 to 123 or claim 183 or claim 184 for the preparation of a medicament for regulating glucocorticoid production.

191. A method for the treatment of a condition which is improved by the activation of the MC2 receptor, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 123 or claim 183 or claim 184.

192. A method for regulating glucocorticoid production, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 123 or claim 183 or claim 184.

193. A method according to claim 191 or claim 192, wherein the therapeutically effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, such as

from about 0.1 mg to about 1000 mg, for example from about 0.5 mg to about 500 mg per day.

194. A compound according to any of claims 1 to 123, where the compound is an agonist of the MC3 receptor.

195. A compound according to claim 194, wherein the compound is selective for the MC3 receptor.

196. A pharmaceutical composition comprising a compound according to claim 194 or claim 195.

197. Use of a compound according to any of claims 1 to 123 or claim 194 or claim 195 for increasing the activity of the MC3 receptor.

198. Use of a compound according to any of claims 1 to 123 or claim 194 or claim 195 for treating a condition which is improved by the activation of the MC3 receptor.

199. Use of a compound according to any of claims 1 to 123 or claim 194 or claim 195 for the preparation of a medicament for treating a condition which is improved by the activation of the MC3 receptor.

200. Use according to claim 198 or claim 199, wherein the condition to be treated is hypertension.

201. Use according to claim 198 or claim 199, wherein the condition to be treated is overweight or obesity.

202. Use according to claim 198 or claim 199, wherein the condition to be treated is sexual dysfunction.

203. Use of a compound according to any of claims 1 to 123 or claim 194 or claim 195 for reducing blood pressure and heart rate or for inducing natriuresis.

204. Use of a compound according to any of claims 1 to 123 or claim 194 or claim 195 for the preparation of a medicament for reducing blood pressure and heart rate or for inducing natriuresis.

205. A method for the treatment of a condition which is improved by the activation of the MC3 receptor, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 123 or claim 194 or claim 195.

206. A method for the treatment of hypertension, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 123 or claim 194 or claim 195.

207. A method for the treatment of overweight or obesity, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 123 or claim 194 or claim 195.

208. A method for the treatment of sexual dysfunction, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 123 or claim 194 or claim 195.

209. A method according to any of claims 205 to 208, wherein the therapeutically effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, such as from about 0.1 mg to about 1000 mg, for example from about 0.5 mg to about 500 mg per day.

210. A compound according to any of claims 1 to 123, where the compound is an agonist of the MC5 receptor.

211. A compound according to claim 210, wherein the compound is selective for the MC5 receptor.

212. A pharmaceutical composition comprising a compound according to claim 210 or claim 211.

213. Use of a compound according to any of claims 1 to 123 or claim 210 or claim 211 for increasing the activity of the MC5 receptor.

214. Use of a compound according to any of claims 1 to 123 or claim 210 or claim 211 for treating a condition which is improved by the activation of the MC5 receptor.

215. Use of a compound according to any of claims 1 to 123 or claim 210 or claim 211 for the preparation of a medicament for treating a condition which is improved by the activation of the MC5 receptor.

216. Use according to claim 214 or claim 215, wherein the condition to be treated is hypertension.

217. Use of a compound according to any of claims 1 to 123 or claim 210 or claim 211 for regulating exocrine gland secretion, for regulating aldosterone secretion, for suppressing stress-induced alarm substances, or for stimulating exocrine glands, cardiac and testicular functions.

218. Use of a compound according to any of claims 1 to 123 or claim 210 or claim 211 for the preparation of a medicament for regulating exocrine gland secretion, for regulating aldosterone secretion, for suppressing stress-induced alarm substances, or for stimulating exocrine glands, cardiac and testicular functions.

219. A method for the treatment of a condition which is improved by the activation of the MC5 receptor, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 123 or claim 210 or claim 211.

220. A method for treatment of hypertension, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 123 or claim 210 or claim 211.

221. A method for regulating exocrine gland secretion, for regulating aldosterone secretion, for suppressing stress-induced alarm substances, or for stimulating exocrine glands, cardiac and testicular functions, the method comprising administering to a subject in need thereof a

therapeutically effective amount of a compound according to any of claims 1 to 123 or claim 210 or claim 211.

222. A method according to any of claims 219 to 221, wherein the therapeutically effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, such as from about 0.1 mg to about 1000 mg, for example from about 0.5 mg to about 500 mg per day.

223. A compound according to any of claims 1 to 123, where the compound is an agonist of the MC3 receptor and the MC4 receptor.

224. A compound according to claim 223, wherein the compound is selective for the MC3 and MC4 receptor.

225. A pharmaceutical composition comprising a compound according to claim 223 or claim 224.

226. Use of a compound according to claim 223 or claim 224 for increasing the activity of the MC3 receptor.

227. Use of a compound according to claim 223 or claim 224 for increasing the activity of the MC4 receptor.

228. Use according to claim 226 or claim 227 for increasing the activity of the MC3 receptor and increasing the activity of the MC4 receptor.

229. Use of a compound according to claim 223 or claim 224 for treating a condition which is improved by the activation of the MC3 receptor.

230. Use of a compound according to claim 223 or claim 224 for treating a condition which is improved by the activation of the MC4 receptor.

231. Use of a compound according to claim 223 or claim 224 for treating a condition which is improved by the activation of the MC3 receptor and by the activation of the MC4 receptor.

232. Use of a compound according to claim 223 or claim 224 for the preparation of a medicament for treating a condition which is improved by the activation of the MC3 receptor.

233. Use of a compound according to claim 223 or claim 224 for the preparation of a medicament for treating a condition which is improved by the activation of the MC4 receptor.

234. Use of a compound according to claim 223 or claim 224 for the preparation of a medicament for treating a condition which is improved by the activation of the MC3 receptor and by the activation of the MC4 receptor.

235. Use according to any of claims 229 to 234, wherein the condition to be treated is overweight or obesity.

236. Use according to any of claims 229 to 234, wherein the condition to be treated is sexual dysfunction.

237. A method for the treatment of a condition which is improved by the activation of the MC3 receptor, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to claim 223 or claim 224.

238. A method for the treatment of a condition which is improved by the activation of the MC4 receptor, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to claim 223 or claim 224.

239. A method for the treatment of a condition which is improved by the activation of the MC3 receptor and by the activation of the MC4 receptor, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to claim 223 or claim 224.

240. A method for the treatment of overweight or obesity, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to claim 223 or claim 224.

241. A method for the treatment of sexual dysfunction, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to claim 223 or claim 224.

242. A method according to any of claims 237 to 241, wherein the therapeutically effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, such as from about 0.1 mg to about 1000 mg, for example from about 0.5 mg to about 500 mg per day.

243. A compound according to any of claims 1 to 123, where the compound is an agonist of the MC3 receptor and the MC5 receptor..

244. A compound according to claim 243, wherein the compound is selective for the MC3 and MC5 receptor.

245. A pharmaceutical composition comprising a compound according to claim 243 or claim 244.

246. Use of a compound according to claim 243 or claim 244 for increasing the activity of the MC3 receptor.

247. Use of a compound according to claim 243 or claim 244 for increasing the activity of the MC5 receptor.

248. Use according to claim 246 or claim 247 for increasing the activity of the MC3 receptor and increasing the activity of the MC5 receptor.

249. Use of a compound according to claim 243 or claim 244 for treating a condition which is improved by the activation of the MC3 receptor.

250. Use of a compound according to claim 243 or claim 244 for treating a condition which is improved by the activation of the MC5 receptor.

251. Use of a compound according to claim 243 or claim 244 for treating a condition which is improved by the activation of the MC3 receptor and by the activation of the MC5 receptor.

252. Use of a compound according to claim 243 or claim 244 for the preparation of a medicament for treating a condition which is improved by the activation of the MC3 receptor.

253. Use of a compound according to claim 243 or claim 244 for the preparation of a medicament for treating a condition which is improved by the activation of the MC5 receptor.

254. Use of a compound according to claim 243 or claim 244 for the preparation of a medicament for treating a condition which is improved by the activation of the MC3 receptor and by the activation of the MC5 receptor.

255. Use according to any of claims 249 to 254, wherein the condition to be treated is hypertension.

256. A method for the treatment of a condition which is improved by the activation of the MC3 receptor, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to claim 243 or claim 244.

257. A method for the treatment of a condition which is improved by the activation of the MC5 receptor, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to claim 243 or claim 244.

258. A method for the treatment of a condition which is improved by the activation of the MC3 receptor and by the activation of the MC5 receptor, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to claim 243 or claim 244.

259. A method for the treatment of hypertension, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to claim 243 or claim 244.

260. A method according to any of claims 256 to 259, wherein the therapeutically effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, such as from about 0.1 mg to about 1000 mg, for example from about 0.5 mg to about 500 mg per day.

261. Use of a compound according to any of claims 1 to 123 for increasing antipyretic activity.

262. Use of a compound according to any of claims 1 to 123 for the preparation of a medicament for increasing antipyretic activity.

263. A method for increasing antipyretic activity, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 123.

264. A method according to claim 263, wherein the therapeutically effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, such as from about 0.1 mg to about 1000 mg, for example from about 0.5 mg to about 500 mg per day.

265. Use of a compound according to any of claims 1 to 123 for inducing lipolysis.

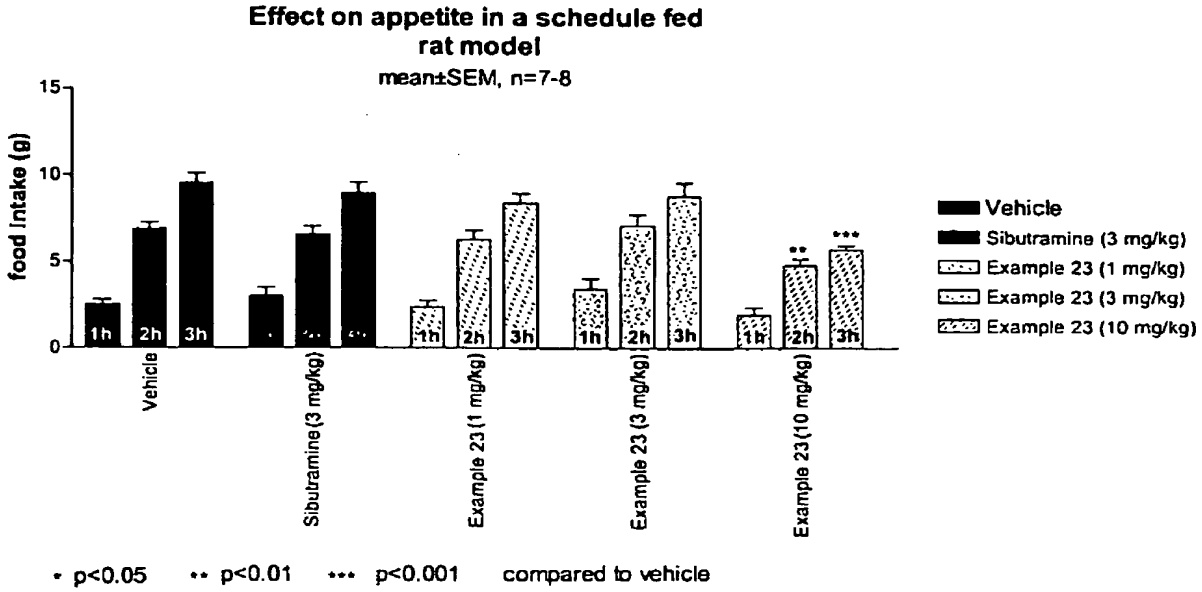
266. Use of a compound according to any of claims 1 to 123 for the preparation of a medicament for inducing lipolysis.

267. A method for inducing lipolysis, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any of claims 1 to 123.

268. A method according to claim 267, wherein the therapeutically effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg, such as from about 0.1 mg to about 1000 mg, for example from about 0.5 mg to about 500 mg per day.

FIG 1/1

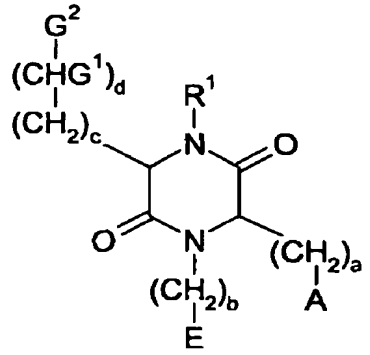
FIGURE 1



* p<0.05

ABSTRACT

The present invention relates to novel compounds of the general formula (I),



Formula (I)

as well as any optical or geometric isomer or tautomer form thereof, or a pharmaeutically acceptable salt thereof, as agonists of melanocortin receptors, such as as agonists of the MC4 receptor. The compounds may for instance be used in the treatment of obesity.